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## Long-term Mental Well-being of Adolescents and Young Adults Diagnosed with Venous Thromboembolism

*a multistage mixed methods study*

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**LONG-TERM MENTAL WELL-BEING OF  
ADOLESCENTS AND YOUNG ADULTS  
DIAGNOSED WITH  
VENOUS THROMBOEMBOLISM**

A MULTISTAGE MIXED METHODS STUDY

**BY  
ANETTE ARBJERG HØJEN**

DISSERTATION SUBMITTED 2016



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Anette Arbjerg Højen



**AALBORG UNIVERSITY**  
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## ENGLISH SUMMARY

Worldwide, venous thromboembolism (VTE) remains a major cause of mortality and morbidity. Although VTE is less common in young age compared to older age, evidence suggests that young VTE patients, in particular, are at risk of psychological distress and impaired mental well-being. Thus, the intent of this multistage mixed methods study was to investigate the long-term mental well-being of adolescents and young adults diagnosed with VTE. This was sought through epidemiological descriptions of the long-term mental well-being using psychotropic drug purchase as a proxy; qualitative exploration of the lived experiences following VTE; epidemiological comparisons of the long-term mental well-being between adolescents and young adults with VTE and insulin dependent diabetes mellitus (IDDM) using psychotropic drug purchase as a proxy and finally; an integrated mixed methods interpretation combining the description, exploration and comparison. The description showed the mental well-being of adolescents and young adults was negatively impacted in long-term when considering psychotropic drug purchase as a proxy. One in five adolescents and young adults diagnosed with VTE redeemed a psychotropic drug prescription within the first 5 years after diagnosis. A risk double that of age and sex matched peers. The exploration of the lived experiences following VTE showed an experience of; a creeping loss of youth immortality, a perception of being different; to live with a body in a state of alarm; and to feel symptom management insecurity. The comparison showed the long-term mental well-being of adolescents and young adults with VTE was worse than that of chronically ill patients with IDDM when considering risk of psychotropic drug purchase as a proxy. The integrated mixed methods interpretation of the findings combining the description exploration and comparison showed the mental well-being of adolescents and young adults diagnosed with VTE had a chronic perspective with an increased risk of psychotropic drug purchase and psychological distress persisting over time. Impaired mental well-being was largely connected to fear of recurrence and concomitant uncertainty. Thus to navigate uncertainty was important for the long-term mental well-being. Further, the integrated mixed methods interpretation showed the perceived health threat played a more profound role than illness severity for the long-term mental well-being. In conclusion, mental well-being of adolescence and young adults diagnosed with VTE is negatively impacted in the long-term, which highlights the clinical importance of long-term focus on mental well-being in this group.



## DANSK RESUME

På verdensplan er venøs tromboemboli (VTE) en vigtig årsag til mortalitet og morbiditet. På trods af at VTE er mindre udbredt hos unge end hos ældre peger forskningen på at særligt unge patienter med VTE har en øget risiko for et svækket mentalt velbefindende. Formålet med dette multistage mixed methods study var derfor, at undersøge det langsigtede mentale velbefindende hos unge og unge voksne diagnosticeret med VTE. Dette blev undersøgt gennem; for det første epidemiologiske beskrivelser af det langsigtede mentale velbefindende med anvendelse af psykofarmaka køb som proxy; for det andet kvalitativ eksplorering af unge og unge voksnes levede erfaringer efter en VTE diagnose; for det tredje epidemiologisk sammenligning af det langsigtede mentale velbefindende hos unge og unge voksne med henholdsvis VTE og insulin-afhængig diabetes med anvendelse af psykofarmaka køb som proxy og endeligt; for det fjerde en integreret mixed methods interpretation, hvor beskrivelsen, eksploreringen og sammenligningen blev kombineret. Den epidemiologiske beskrivelse viste, at unge og unge voksnes mentale velbefindende var negativt påvirket på lang sigt ved psykofarmaka køb anvendt som proxy. En ud af fem unge og unge voksne diagnosticeret med VTE havde inden for 5 år efter diagnosen indløst en recept på psykofarmaka. En risiko der var dobbelt så stor som hos deres jævnaldrende matchet på alder og køn. Den kvalitative eksplorering af de unge og unge voksnes levede erfaringer viste en oplevelse af; et krybende tab af ungdommens udødelighed; at opleve sig anderledes; at leve med en krop i alarmberedskab; og en utryk symptomhåndtering. Den epidemiologiske sammenligning viste, at det langsigtede mentale velbefindende hos unge og unge voksne med VTE var dårligere end unge kronisk syge personer med insulin-afhængig diabetes når psykofarmaka køb blev anvendt som proxy. Den integrerede mixed methods interpretation af fundene, hvor beskrivelsen, eksploreringen og sammenligningen blev kombineret viste at det langsigtede mentale velbefindende hos unge og unge voksne diagnosticeret med VTE havde et kronisk perspektiv, hvor en øget risiko for psykofarmaka køb og svækket mentalt velbefindende vedblev med at eksistere over tid. Det svækkede mentale velbefindende var i særlig grad relateret til frykten for tilbagefald og den medfølgende usikkerhed. At navigere i usikkerheden var derfor vigtigt for det mentale velbefindende. Endvidere viste den integrerede mixed methods interpretation, at den oplevede trussel på sundheden og livet spillede en større rolle for det mentale velbefindende end den fysiologiske alvorlighed af VTE. Det konkluderes at det mentale velbefindende hos unge og unge voksne diagnosticeret med VTE er negativt påvirket på lang sigt, hvilket fremhæver den kliniske relevans af et langsigtet fokus på at fremme det mentale velbefindende hos denne gruppe af patienter.

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*Anette Arbjerg Højen*

# TABLE OF CONTENTS

<b>CHAPTER 1. Introduction.....</b>	<b>11</b>
1.1. Venous thromboembolism and mental well-being .....	11
1.2. Venous thromboembolism in adolescence and young adulthood.....	12
<b>CHAPTER 2. Background.....</b>	<b>15</b>
2.1. Literature review .....	15
2.2. Summery and rational for this research.....	20
<b>CHAPTER 3. Aim and objectives .....</b>	<b>23</b>
<b>CHAPTER 4. Research design .....</b>	<b>25</b>
4.1. Pragmatism .....	25
4.2. Multistage mixed methods framework .....	26
4.3. Materials and Methods .....	28
4.3.1. Register data sources .....	28
4.3.2. Statistical analysis .....	29
4.3.3. Development of interview guides .....	30
4.3.4. Interviews .....	31
4.3.5. A phenomenological hermeneutical Interpretation approach .....	32
4.4. Ethical considerations.....	35
<b>CHAPTER 5. Results.....</b>	<b>37</b>
5.1. Study 1: Description of long-term mental well-being of adolescents or young audlts diagnosed with VTE .....	37
5.2. Study 2: Exploration of the essential meaning of adoles-cents and young adults lived experiences following VTE .....	39
5.3. Study 3: Comparison of long-term mental well-being following VTE versus IDDM in adolescents and young adulthood .....	44
5.4. Integrated mixed methods interperatation .....	46
5.4.1. Chronic timeline perspective - Fear of recurrence and a strive for normalisation.....	46
5.4.2. Navigating uncertainty.....	48
5.4.3. Perceived health threat versus illness severity .....	49
<b>CHAPTER 6. Discussion.....</b>	<b>51</b>

6.1. Discussion of findings .....	51
6.2. Methodological considerations .....	54
6.2.1. Mixed methods .....	54
6.2.2. Study 1 and Study 3 .....	56
6.2.3. Study 2 .....	58
6.2.4. The generalisability and transferability of the results .....	60
<b>CHAPTER 7. Conclusion.....</b>	<b>63</b>
<b>CHAPTER 8. Implications and Perspectivs .....</b>	<b>65</b>
<b>Literature list .....</b>	<b>67</b>
<b>Appendices .....</b>	<b>77</b>

## ABBREVIATIONS

BDI: Beck Depression Inventory

BIPQ: The Brief Illness Perceptions Questionnaire

CI: confidence interval

DVT: deep venous thrombosis

HADS: The Hospital Anxiety and Depression Scale

HAI: The Health and Anxiety Inventory

IDDM: insulin dependent diabetes mellitus

PE: pulmonary embolism

PedQL 4.0: Paediatric Quality of Life Inventory version 4.

PTSD: posttraumatic stress disorder

QoL: quality of life

R-IES: Revised Impact of Event Scale

SF-12: 12-Item Short-Form Health Survey

SF-36: 36-Item Short-Form Health Survey

STAI: State-Trait Anxiety Inventory

VEINES-QOL/Sym: The Venous Insufficiency Epidemiological and Economic Study quality of life and symptoms questionnaire,

VTE-TB: VTE Treatment Beliefs

VTE: venous thromboembolism

# CHAPTER 1. INTRODUCTION

*“With poor adjustment, the patient may become restless and moody. He may develop an attitude towards life that is negative and generally dissatisfied. Indeed, the patient may plunge into a pronounced depression with his functioning at only a fraction of his presickness level.”<sup>1</sup>*

This was concluded in 1976 by Griffith and Hero<sup>1</sup> in a case report of a young man suffering a pulmonary embolism at the age of 26. Clinical descriptions from the last 3 decades and narratives on various thrombosis internet sites illustrate how venous thromboembolism (VTE) in adolescence and young adulthood may have a detrimental impact on mental well-being.<sup>1-3</sup> Decreased quality of life (QoL), anxiety, and depression have been reported as long-term consequences of VTE traditionally considered a short-term illness.<sup>4-7</sup> Adolescents and young adults may be particularly vulnerable as they are in a phase of life creating identities and making decisions in regard of educational path, career, and family.<sup>8</sup> With this as the point of origin, this thesis will address the long-term mental well-being of adolescents and young adults diagnosed with VTE.

## 1.1. VENOUS THROMBOEMBOLISM AND MENTAL WELL-BEING

Worldwide, VTE remains a major cause of mortality and morbidity affecting 1-2 per 1000 persons each year.<sup>9</sup> VTE encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT commonly occurs in the lower extremities, and PE is usually the result of the thrombus embolising and becoming lodged in the pulmonary arteries. Of patients with symptomatic VTE approximately one third manifests PE and two thirds manifest DVT alone.<sup>10</sup> VTE can occur unprovoked with no identifiable cause or provoked by transient or persistent risk factors, and three conditions are thought to predispose to the thrombus formation collectively known as Vichow’s triad; alteration of blood flow; vascular endothelial injury and; alteration in the constituents of the blood.<sup>11</sup> VTE is traditionally considered a short-term illness, but long-term consequences of VTE are well-documented. The two major consequences of VTE include recurrence and post-thrombotic syndrome. The risk of recurrence has been demonstrated to exceed 50 % over 10 years for patients who suffer unprovoked VTE if not receiving anticoagulant treatment and 20 % over 10 years for patients who suffer VTE with an identifiable provoking factor.<sup>12</sup> The post-thrombotic syndrome occurs as a complication in 25 % to 50 % of patients with DVT within 1 to 2 years of the event, a chronic disorder characterised by pain, vein dilation, oedema, skin pigmentation, and in severe cases skin ulceration.<sup>13</sup> Furthermore, approximately 1 % to 4 % of patients with PE will develop chronic thromboembolic pulmonary

hypertension.<sup>14,15</sup> These complications leads to suffering, disability and is costly to society, which exceeds the physical consequences alone.<sup>13,14,16</sup> Development of post thrombotic syndrome is considered an important determinant of long-term QOL. Patients with post thrombotic syndrome report QOL that is poorer than patients with arthritis or diabetes, and QOL in patients with severe post thrombotic syndrome is comparable to persons with cancer or congestive heart failure.<sup>4</sup>

While the physical consequences of VTE have been widely discussed within the scientific context of VTE, the subsequent mental well-being has received less attention. However, elevated levels of anxiety and depression symptoms have been reported among VTE patients in the immediate time following VTE,<sup>17,18</sup> and in long-term.<sup>7,19</sup> Studies examining QOL of VTE patients have also provided information about subjective mental and physical health.<sup>4-6,20</sup> In general, revealing a decline in QOL after the VTE event with a subsequent improvement although less pronounced when considering the mental component of QOL alone.<sup>4-6,20</sup> Further, patients are reported to experience symptomatic PE as a life-changing distressing event, leading to behaviour modification, in some cases characteristic of PTSD.<sup>21</sup> Thus, existing evidence suggests the mental well-being of patients with VTE is negatively affected.

Mental well-being was introduced by WHO<sup>22</sup> in 1948 as a central part of the definition on health, and was later described as *'a state of well-being in which the individual realises his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community'*.<sup>23</sup> Thus, mental well-being is a complex construct, determined by a multiplicity of factors including biological, individual, family and social as well as economic and environmental conditions.<sup>24</sup> Poorer mental well-being in chronically ill patients is connected to; decreased treatment adherence; increased disability and symptom burden as well as; higher complication rates and risk of death etc.<sup>25,26</sup> Indeed, results from the thrombEVAL study recently showed symptoms of anxiety and depression among patients treated with oral anticoagulation with vitamin K antagonists, were associated with increased mortality, and impaired several aspects of anticoagulant treatment.<sup>27,28</sup> Thus, mental well-being possibly plays an important role for disease management as well as long-term prognosis in patients with VTE.

## 1.2. VENOUS THROMBOEMBOLISM IN ADOLESCENCE AND YOUNG ADULTHOOD

VTE is an illness that affects the young and the old. However, the incidence of VTE increases with age, approximately doubling with each decade.<sup>29</sup> VTE is therefore less common in young age with an incidence rate of 3.2 per 10.000

person-years for patients < 30 year.<sup>29</sup> Hence, the burden of VTE is not confined to the elderly, and adolescents and young adults may be particularly vulnerable to distress and disrupted mental well-being. From a transition theory perspective, adolescents and young adults will face multiple and simultaneous transitions, enhancing the risk of a disrupted sense of balance and well-being.<sup>30</sup> The health-illness transition of VTE involves potentially stressful illness adaption.<sup>31</sup> In addition to the potential complications of post thrombotic syndrome and pulmonary hypotension which are also reported in younger populations<sup>14,32</sup>, adolescents and young adults with VTE live with increased long-term mortality and the perpetual risk of recurrent VTE - a risk that was recently shown to be highest in the younger population.<sup>29,33</sup> For the young girls highly relevant in terms of a possible pregnancy, as the risk of VTE increased substantially during pregnancy and in the post-natal period.<sup>34,35</sup> Further, adolescents and young adults with VTE will also have to manage the careful and regular monitoring of anticoagulant treatment in a shorter or longer period of time. An important task as non-compliance with anticoagulant therapy is associated with increased long-term mortality.<sup>36</sup> Furthermore, this poses a particular challenge among adolescents and young adults as strong evidence exists that adherence with treatment regimen in this group is a major problem.<sup>37</sup>

In addition to the health-illness transition adolescents and young adults will be facing developmental transitions. Adolescence as a developmental transition is marked by identity formation and growing independence, and involves many significant biological, psychological, and social changes.<sup>8</sup> Identity formation continues into young adulthood, where independence grows stronger and includes developmental transition marked by intimacy, parenthood and career consolidation. Tasks, which today often continues into the early thirties. In Denmark there is a dividing line around the age of 33 in regards of the portion of people who; have a permeant job; own private property; is with a partner and; have kids.<sup>38-40</sup> In 2014 the average age of first-time motherhood was 29.1 years and of first time fatherhood 31.4 years. Whereas the average age of first time marriage for women was 32.2 years and for men 34.8 years.<sup>38</sup> Thus, the period between childhood and self-supporting adulthood have become longer with the developmental transitions of young adulthood continuing into the early thirties. The simultaneous health-illness and developmental transitions increases complexity and thereby enhances vulnerability to distress, confusion and instability.<sup>30</sup> Accordingly, extensive research have produced clear evidence that chronic physical illness e.g. diabetes in adolescence or young adulthood can result in significant long-term psychological, emotional, and behavioural problems.<sup>41,42</sup> Thus, adolescents and young adults diagnosed with VTE may be particular vulnerable to psychological distress and impaired mental well-being.





## CHAPTER 2. BACKGROUND

### 2.1. LITERATURE REVIEW

To provide an overview of existing knowledge on the mental well-being following VTE in adolescence or young adulthood a literature review of the peer-reviewed and grey literature was conducted. Studies were required to meet the following criteria; (1) The study includes adolescents or young adults; (2) participants have been diagnosed with DVT, PE or both; (3) the study includes psychosocial dimensions; (4) the study is published in English or Nordic language. To ensure a systematic and exhaustive review of the literature a research librarian at the Medical Library in Aalborg University Hospital assisted the search. The following electronic bibliographic databases were systematically searched: PubMed, Cinahl, ProQuest (including Psych-INFO) and Web of Science. MeSH and equivalent terms was used when applicable and the search strategy employed was as follows:

**Adolescent OR Age factors OR Young Adult OR Youth**

AND

**Venous Thromboembolism OR Pulmonary Embolism OR  
Venous Thrombosis OR Embolism and Thrombosis**

AND

**Psychology OR Psychology[Subheading] OR Quality of Life OR  
Mental Health OR Depression OR Anxiety**

Furthermore, citation searches were conducted both manually and in the citation database Scopus. To cover potentially relevant grey literature internet searches were conducted for reports, theses and books.

A total of 13 studies meeting the inclusion criteria were identified. Studies excluded; pertained no age specific information; assessed the relationship between psychiatric disorders and the risk of subsequent venous thromboembolism and; developed measurement tools. The literature review revealed that most studies assessed QoL (n=6)<sup>4,43–47</sup> or anxiety, depression and other psychosocial measurements (n=3)<sup>7,17,48</sup> or a combination hereof (n=2).<sup>6,18</sup> The remaining two studies were qualitative interview studies the first<sup>21</sup> exploring the psychological consequences of PE and the second<sup>49</sup> exploring patients and relatives' perceptions, knowledge and concerns regarding VTE risk. Four of the studies focused on patients diagnosed with VTE at a younger age. One included children, adolescents and young adults;<sup>44</sup> two concerned

pregnancy related DVT,<sup>45,46</sup> and; one defined younger age  $\leq 45$ .<sup>48</sup> Thus, the literature focused on mental well-being following VTE in adolescence or young adulthood specifically is sparse. **Table 1** presents an overview of authors, aims, designs and participants of the 13 identified studies, while the results will be summarised in the following section.

**Table 1.** A summary of publications on mental well-being following VTE in adolescence or young adulthood

Author, year, and country	Aim	Design	Participants
<i>Haxaire et al.</i> 2015, France	To examine patients and family members' perception, knowledge and concerns towards VTE risk.	Qualitative interview study. <u>Data analysis</u> Combination of thematic analysis and constant comparison.	<u>VTE type</u> DVT/PE <u>N</u> = 10 (VTE patients) <u>Age</u> Mean(range) 37.2(24-60) <u>Time since VTE</u> , Unclear
<i>Marvig et al.</i> 2015, Greece, Netherlands, Sweden, UK	To evaluate QoL immediately after the start of anticoagulant therapy, and after three months of treatment, in newly diagnosed patients with VTE or atrial fibrillation.	Prospective cohort study. QoL was assessed at baseline, and 3 months after DVT. <u>Outcome measures</u> EuroQoL 5 dimensions	<u>VTE type</u> DVT/PE <u>N</u> = 847 (187 VTE patients) <u>Age</u> VTE patients Mean(range) 57(22-90) <u>Time since VTE</u> <3 months
<i>Bennett et al.</i> 2014, Wales UK	To identify psychosocial factors associated with post-traumatic stress and health anxiety following VTE.	Cross-sectional study. <u>Outcome measures</u> Subjective Threat Scale, Threat reappraisal, Dissociation, BIPQ, R-IES, HAI and VTE-TB	<u>VTE type</u> DVT/PE <u>N</u> = 158 <u>Age</u> Mean(SD) 40.5(12.26) <u>Time since VTE</u> Mean(SD) 25.6 (33.78) months
<i>Noble et al.</i> 2014, Wales UK	To explore the psychological consequences of symptomatic PE.	Qualitative interview study. <u>Data analysis</u> Interpretative phenomenological analysis.	<u>VTE type</u> PE <u>N</u> = 9 <u>Age</u> Mean(range) 45(26-72) <u>Time since VTE</u> Mean(range) 24(9-60) months
<i>Kumar et al.</i> 2014, USA	To evaluate the association between post thrombotic syndrome and QoL in children and young adults with DVT.	Cross-sectional study. <u>Outcome measures</u> Validated post thrombotic syndrome survey instrument and PedsQL 4.0	<u>VTE type</u> DVT <u>N</u> = 90 <u>Age</u> Mean(SD) 19.3 (7.7) <u>Time since VTE</u> Mean(SD) 6.5(4.6) years
<i>Wik et al.</i> 2012, Norway	To assess predictors and long-term frequency of post-thrombotic syndrome after pregnancy-related VTE	Cross-sectional study. <u>Outcome measures</u> Villalta scores, VEINES-QOL/Sym	<u>VTE type</u> DVT/PE <u>N</u> = 274 <u>Age</u> Range 22-59 <u>Time since VTE</u> Mean(range) 9.1 (3-16) years
<i>Liu et al.</i> 2011, China	To investigate levels of depression and anxiety in acute pulmonary embolism patients.	Cross-sectional study. <u>Outcome measures</u> BDI and STAI	<u>VTE type</u> PE <u>N</u> = 60 <u>Age</u> Mean(range) 52 (25-75) <u>Time since VTE</u> < 1 week

<i>Wik et al.</i> 2011, Norway	To evaluate the long-term consequences of pregnancy-related DVT.	Cross-sectional study. <u>Outcome measures</u> VEINES-QoL/Sym	<u>VTE type</u> DVT N = 208 <u>Age</u> Range 22-59 <u>Time since VTE</u> Mean(range) 9.5(3-16) years
<i>Lukas et al.</i> 2009, Switzerland	To investigate the relationship of QoL with psychological variables in patients with VTE.	Cross-sectional study <u>Outcome measures</u> SF-12 and HADS	<u>VTE type</u> DVT/PE N = 205 <u>Age</u> Mean(range) 47.4(18-80) <u>Time since VTE</u> Mean(range) 20.8(4-430) months
<i>Kahn et al.</i> 2008, Canada	To measure change in QoL during the 2 years after a DVT diagnosis	Prospective cohort study. QoL was assessed at baseline, 1, 4, 8, 12 and 24 months after DVT. <u>Outcome measures</u> SF-36 and [VEINES-QoL/Sym	<u>VTE type</u> DVT N = 387 <u>Age</u> Mean(range) 56(21-96) <u>Time since VTE</u> ≤ 24 months
<i>Fiandaca et al.</i> 2006, Italy	To assess psychological, social and familial functioning and coping styles in young adults following a single episode of venous or arterial thrombosis.	Cross-sectional study <u>Outcome measures</u> BDI; Battle culture free adult self-esteem; Family assessment device; Recent life event schedule; Revised ways of coping checklist and; Work leisure and family life.	<u>VTE type</u> DVT/PE N = 50 (34 VTE patients) <u>Age</u> Mean(range) 32.3(19-45) <u>Time since VTE</u> Mean(range) 5.4(3-16) months
<i>Moore et al.</i> 2006, England UK	To examine patients' reactions to venous thrombosis	Cross-sectional study <u>Outcome measures</u> SF-12, HADS. Thrombosis worries, examined using a disease-specific adapted version of breast cancer worries scale.	<u>VTE type</u> DVT/PE N = 123 <u>Age</u> Mean(range) 52.5(16-84) <u>Time since VTE</u> < 1 months
<i>Kahn et al.</i> 2005, Canada	To evaluate QoL after DVT	Prospective cohort study. QoL assessed at baseline, 1 and 4 months. <u>Outcome measures</u> SF-36, VEINES-QoL/SYM	<u>VTE type</u> DVT N = 359 <u>Age</u> Mean(SD) 55.8(14.8) <u>Time since VTE</u> ≤ 4 months

### Anxiety depression and other psychosocial measures

The existing literature on mental well-being following a VTE diagnosis in adolescence or young adulthood reviled information on anxiety, depression, and other psychological measures, primarily in short-term. Moore et al.<sup>18</sup> examined patients' reactions to VTE within the first month after the event. Younger age was reported a significant predictor of thrombosis worries and symptoms of anxiety but not depression, when assessed on The Hospital Anxiety and Depression Scale. Concurrently, age was reported to be independently inversely related to anxiety symptoms, in a cross-sectional study by Liu et al.<sup>17</sup>, investigating the levels of depression (BDI score) and anxiety (STAI score) within the first week of acute symptomatic PE. Thus, indicating higher levels of anxiety among the younger VTE patients. Fiandaca et al.<sup>48</sup> assessed psychological, social, and familial functioning in young adults (aged 19-45) following venous thromboembolism or arterial thrombosis 3-16 months after the event (mean time range 5.4 months). Thus, beyond the immediate period following VTE Fiandaca et al.<sup>48</sup> reported greater

psychological impairment in individuals < 34 years compared with those  $\geq$  34 years. Compared to healthy controls, young patients with thrombosis had lower self-esteem, showed higher impairment in social activities and in familial relationships, and used more frequently coping strategies to manage difficult situations. The time elapsed from the event until the assessment did not influence the results. In contrary, levels of health related anxiety (HAI score) and impact of event (R-IES score) were not found to be associated with age, in a cross sectional study by Bennett et al.<sup>7</sup> with a mean time range since VTE of 25.8 months. However, the mean age of the VTE patients in this study was low (40.5 years), and the overall mean scores of both the R-IES and HAI were reported above the cut-off score for likely PTSD and illness anxiety disorder. Thus, indicating a possibility of high levels of psychological distress and anxiety also in long term, within a population of younger VTE patients.

### Quality of life

The literature review revealed age specific information in a number of studies addressing QOL post VTE. The assessments included both disease-specific<sup>18,46</sup> and generic<sup>6,43,44</sup> QOL measurements as well as a combination of the two.<sup>4,50</sup> In a prospective cohort study, part of the Venous Thrombosis Outcomes study, Kahn et. al.<sup>47</sup> evaluated QOL after DVT. They found age not to be predictive of SF-36 scores from 1-4 months. However, in a later evaluation at 2-year follow-up Kahn et al.<sup>51</sup> reported age an independent predictor of SF-36 scores, in the sense that the Physical Component Summary score decreased and the Mental Component score increased with increasing age. Thus, indicating worse physical QOL but better mental QOL with increasing age. In concurrence with these findings, Lukas et al.<sup>6</sup> found lower SF-12 Physical Component Summary scores and higher Mental Component Summary scores with increasing age, when investigating the relationship between QOL and psychological variables in patients with VTE (mean time range since VTE of 20.8 months).

As part of the European pharmacogenetics of anticoagulant treatment (EU-PACT) Marvig et al.<sup>43</sup> evaluated QOL immediately after the start of anticoagulant therapy, and after three months of treatment, in newly diagnosed patients with VTE or atrial fibrillation. Among the patients with VTE, QOL improved with increasing age, displaying lower QOL scores (EQ-Index score) among the younger age groups (aged 22-49) compared to the older age groups (aged 50-90) at baseline and follow-up.

### *Post thrombotic syndrome and QOL*

Kumar et al.<sup>44</sup> evaluated the association between post thrombotic syndrome and QoL in children and young adults with DVT in long-term (mean time range since event 6.5 years). Patients with moderate to severe post thrombotic

syndrome reported a significantly lower mean total QOL score (PedsQL) as compared to patients with mild and no post thrombotic syndrome. The physical, social and psychosocial sub-scores were all found significantly lower among patients with post thrombotic syndrome after adjustment for age gender and comorbid conditions, whereas emotional and school sub-scores were found lower, but did not achieved statistical significance.

### *Pregnancy related VTE and Quality of life*

Pregnancy is a profound risk factor for VTE which becomes especially relevant in a population that includes older adolescents and young adults. As part of the Norwegian Venous thrombosis In Pregnancy study, Wik et al.<sup>46</sup> evaluated long-term consequences of pregnancy-related DVT 3-16 years after being diagnosed in the period 1990-2003. Lower QOL scores (VEINES-QOL) were reported in women with previous pregnancy related DVT than controls without DVT matched on date of delivery. Also when adjusted for possible confounders. Thus indicating that pregnancy-related DVT has a negative impact on long-term QOL. In the Norwegian Venous thrombosis In Pregnancy study Wik et al.<sup>45</sup> also assessed the long-term impact of the post thrombotic syndrome, in this part of the study patients with PE were also included. Women with pregnancy related VTE and post thrombotic syndrome were reported to have significantly lower disease-specific QOL (VEINES-QOL) than women with pregnancy related VTE without post thrombotic syndrome. Thus, Wik et al.<sup>45</sup> suggest post thrombotic syndrome may explain in part the poorer QOL following VTE in pregnancy.

### **The experienced mental well-being following VTE**

In a qualitative interview study including patients aged 26-72, Noble et al.<sup>21</sup> explored the psychological consequences of symptomatic PE in long-term (mean time range 24 months). Out of the 9 participants 4 were aged 26-32. Thus identified as young adults. Experiences of the younger participants in terms of quotations were reported in all of the 3 identified themes; life changing experience; post-traumatic stress disorder and; areas of support needs. Uncertainty of future health and not having a cause for the PE were described as an important source of emotional distress and associated with feelings of worry and anxiety. Furthermore, experiences of flashbacks, hypervigilance towards symptoms of recurrent PE, and numbing of memories were described and identified as symptoms suggestive of PTSD. Lastly several areas of support needs were identified including; a lack of attention to psychological care and information giving; empathy and appreciation of the seriousness of their experience from the health care professionals as well as; identification of the potential benefit of support groups.

A recent qualitative interview study by Haxaire et al.<sup>49</sup> examined patients, and family members' perception knowledge and concerns towards VTE risk. The age range of the nine participants were 24-60 years, six of whom were under the age of 33 at the time of the interview. The younger participants experienced VTE as a disruption of everyday life and VTE was linked to symptoms of depression in the identified theme; biographical disruption. Both patients with DVT and PE patients were described to experience difficulties in coping with the event and its consequences. Furthermore, an experience of a delayed diagnosis was described as a cause of distress and persisting anxiety in the theme; initial symptoms and suspicion of VTE.

In the following section the findings of the literature review will be summarized and the rationale for the present study will be presented.

## 2.2. SUMMARY AND RATIONALE FOR THIS RESEARCH

As evidenced in the literature review, existing literature suggests that younger age is associated with increased risk of impaired mental well-being, in terms of decreased mental QOL, depression and anxiety symptoms as well as psychological, social and family functioning. It is indicated this could persist over time. However, the identified studies mainly pertained to mental well-being in shorter term and no studies were identified with primary focus on adolescents and young adults. As laid out in the introduction adolescents and young adults diagnosed with VTE may be particularly vulnerable to distress and impaired mental well-being, of possible great importance for disease management and long-term prognosis. Further, the specific task of youth health and illness is becoming increasingly recognised. The WHO<sup>52</sup> as well as the EU<sup>24</sup> have developed specific strategies in this field, urging development of policies and plans to address young people's health, based on comprehensive, multi-sectorial and evidence-informed health approaches. Thus, thorough research in the specific field of young people's health is thereby recommended. The rationale for this research is therefore to contribute to the current gaps in knowledge with regards to the long-term mental well-being of adolescents and young adults diagnosed with VTE.

The specific age-range of adolescence and young adulthood is often arbitrary set, and definitions and opinions hereon are many.<sup>8,37,53</sup> As put forward in the introduction, the period between the dependence of childhood and independent and self-supporting adulthood have become longer, often continuing into the early thirties. Taking this into account, adolescents and young adults are in the present research defined as persons aged 13-33 years of age.

Mental well-being in its definition encompasses natural and physical dimensions as well as social and psychological dimensions, which accentuates

the necessity of adopting a scientific framework that takes this into account.<sup>24</sup> This suggests the use of a mixed methods design, which draws on the strengths of both qualitative and quantitative methods.





## CHAPTER 3. AIM AND OBJECTIVES

The aim of this mixed methods study was to investigate the long-term mental well-being of adolescents and young adults diagnosed with VTE.

### **Objectives**

To describe the long-term mental well-being of adolescents and young adults diagnosed with VTE using psychotropic drug purchase as a proxy.

To explore the essential meaning of adolescents' and young adults' lived experiences following VTE to gain an in-depth understating of their long-term mental well-being.

To compare long-term mental well-being of adolescents and young adults diagnosed with VTE to that of chronically ill adolescents and young adults diagnosed with insulin dependent diabetes mellitus (IDDM), using psychotropic drug purchase as a proxy.

### **Hypotheses and research questions**

#### *Quantitative hypotheses*

People diagnosed with VTE in adolescence or young adulthood have a higher risk of psychotropic drug purchase than sex and age matched controls.

People diagnosed with VTE in adolescence or young adulthood have a comparable risk of psychotropic drug purchase to that of young chronically ill people diagnosed with IDDM.

#### *Qualitative research question*

What is the essential meaning of the lived experiences of adolescents and young adults following VTE diagnosed in adolescence or young adulthood?

#### *Mixed methods research question*

How can the combination of description, exploration, and comparison expand our understanding of the long-term mental well-being of adolescents and young adults diagnosed with VTE?



## CHAPTER 4. RESEARCH DESIGN

In this section the central ideas of the philosophical assumptions underpinning this research are briefly described. This is followed by a presentation of the multistage mixed methods framework. Although qualitative and quantitative research flow into a mixed methods study the scope of each approach are not to be reduced.<sup>54</sup> Thus, because of the limited space in scientific papers the following section also provide additional information on material and methods of the three papers this thesis is based on. Lastly ethical considerations are described.

### 4.1. PRAGMATISM

Pragmatism is distinguished by the doctrine that both the meaning and the truth of an idea lies in its observable practical consequences.<sup>55</sup> Thus philosophically, pragmatism seeks to address problems not build systems.<sup>56(p143)</sup> As a philosophical tradition pragmatism was founded in the United States during the late nineteenth century by Charles Sanders Peirce and later extended by William James, John Dewey, and George Herbert Mead. All classical pragmatists among those most influential on the diverse variations of pragmatism as a philosophical system.<sup>57</sup>

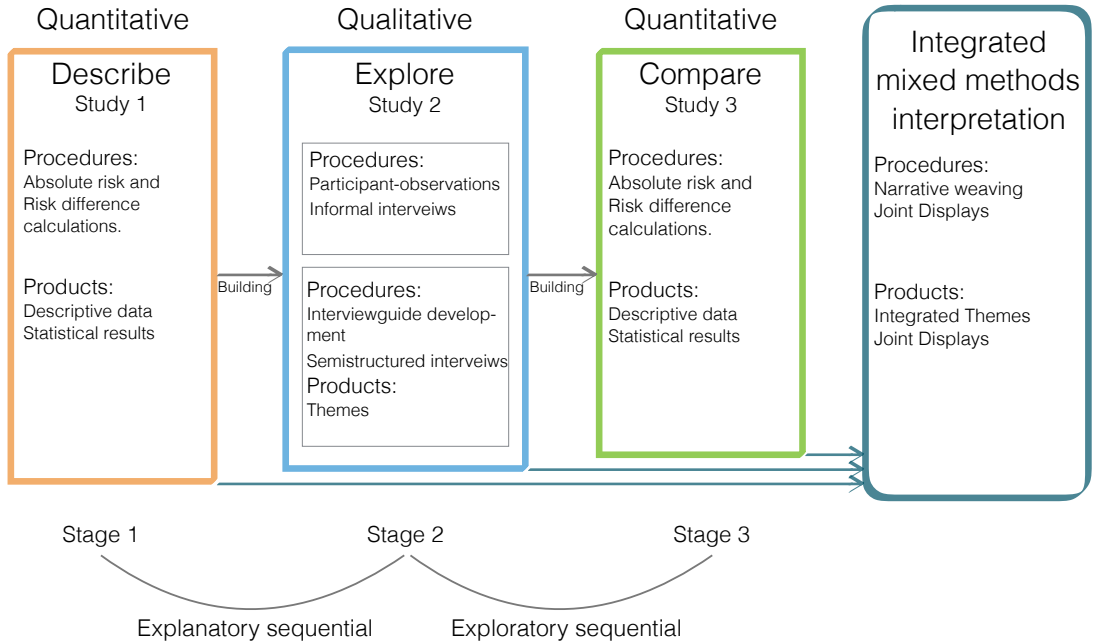
Within pragmatism, knowledge claims arise out of action, situations and consequences rather than ascendant conditions.<sup>56,58</sup> Thus, knowledge is viewed as both constructed and based on the reality of the world we experience and live in. Existence and importance of the natural/physical world as well as the emergent social and psychological world is recognised.<sup>59</sup> The pragmatic position thereby breaks with the traditional dualisms (e.g. positivism and subjectivism). Employing pragmatism as a philosophical underpinning was found relevant when investigating the long-term mental well-being, as mental well-being in its definition encompasses natural and physical dimensions as well as social and psychological dimensions.

From a pragmatic position, different and even conflicting theories and perspectives are considered useful, the pivotal point is to address the problem.<sup>59</sup> Therefore, research approaches should be mixed in the way that offers the best opportunity to answer the research question.<sup>55</sup> In the present study this was employed in a multistage mixed methods framework presented in the following.

## 4.2. MULTISTAGE MIXED METHODS FRAMEWORK

A mixed methods research approach was applied. A keystone in this approach is that both quantitative and qualitative data is collected and analysed, drawing on the strengths of both approaches thereby gaining a better understanding of the research problem than is achievable from either form of data alone.<sup>54,58</sup> In order to achieve this, the focal point of mixed methods research is integration. Via integration-methods the results come together in informative ways producing a sum greater than the individual quantitative and qualitative parts. Often referred to as the integration equation of  $1+1 = 3$ .<sup>54,60</sup> Integration principles and practices are implemented at the design level, the method level and the interpretation and reporting level.<sup>61</sup>

Integration at the design level (the conceptualisation of the study) was accomplished through a multistage mixed methods framework presented in **Figure 1**. It included three stages of data collection. In the first quantitative stage of the study, registry data on psychotropic drug use of adolescents and young adults diagnosed with VTE was used as a proxy to describe the long-term mental well-being. In a multistage framework each stage can comprise several phases,<sup>61</sup> which is true for Stage 2. The second qualitative stage was conducted as a follow-up to the quantitative results. A two-phased data-collection was applied to gain an in-depth understanding of the long-term mental well-being by exploring the essential meaning of the lived experiences of adolescents and young adults diagnosed with VTE. Finally, in the third quantitative stage, as a follow-up to the qualitative results, registry data on psychotropic drug prescriptions were used as a proxy to compare the long-term mental well-being of adolescents and young adults with VTE versus chronically ill young persons with IDDM. Thus, a combination of explanatory and exploratory approaches were used.<sup>61</sup> First an explanatory sequential approach where the quantitative data collection and analyses informed the subsequent qualitative data collection, and secondly an exploratory sequential approach where qualitative data collection and analyses informed the subsequent quantitative data collection.



**Figure 1.** Multistage mixed methods framework

Integration at the method level occurred through linking the methods of data collection and analysis through a building approach.<sup>61</sup> The results from Study 1 informed the data collection approach of Study 2, and the results of Study 2 informed the data collection approach of Study 3.

At the interpretation and reporting level integration occurred through narrative weaving and joint displays presented in the integrated analysis (Chapter 5, section 4). This represent the new insights beyond the information gained from the separate studies.<sup>61</sup> In the narrative weaving approach, the findings from Study 1, 2, and 3 were structured and described thematically with a weaving back and forth of quantitative and qualitative findings by the integrated theme. Joint displays were used as a facilitator and a way to represent the integrated themes visually.<sup>62</sup> Integration on the interpretation and reporting level raises the potential question of coherence of the quantitative and qualitative findings.<sup>61</sup> Therefore, the integration of findings from Study 1, 2 and 3 was inspired by the notion of ‘fit of integration’ with the three following outcomes; 1) *confirmation*, findings from the studies confirm each other; 2) *expansion*, the findings expand insights of the long-term mental well-being, by addressing different aspects hereof and; 3) *discordance*, where the findings of the studies contradict, conflict or disagree with each other.

To sum up, the rationale for the mixed methods design was that an integration of qualitative and quantitative data was needed to investigate the long-term mental well-being of adolescents and young adults diagnosed with VTE.

### **4.3. MATERIALS AND METHODS**

The following section presents additional information on material and methods of Study 1, 2 and 3. This includes for Study 1 and Study 3 register data sources and statistical analysis, and for Study 2 development of interview guides, the interviews, and a phenomenological hermeneutical interpretation approach.

#### **4.3.1. REGISTER DATA SOURCES**

Study 1 and Study 3 were designed as historical population based cohort studies, with linkage between Danish nationwide registries using the unique personal identification number (CPR number) assigned to all Danish residents. CPR is an abbreviation for “Centrale Person Register” the Danish Civil Registration System. Information from the Danish administrative registries was made available for research purposes, by Danish legislation and has been an important tool in healthcare research.<sup>63</sup> In the following the registries used are briefly described.

##### **The Danish Civil Registration System**

The Danish Civil Registration System holds information on sex, date of birth, death, and emigration of all Danish residents.<sup>63,64</sup> National registration of Danish residents was established in 1924 and until 1968 individual information concerning members of each Danish family was registered manually.<sup>63</sup> In 1968 this was replaced by the currently used Danish Civil Registration System where all information is recorded electronically. Once a CPR-number has been assigned, this will not be assigned to other persons, and it will therefore follow the person forever.<sup>64</sup>

##### **The Danish National Patient Registry**

The Danish National Patient Registry, contains information on 99 % of all somatic hospital admissions since 1977 along with diagnosis, coded according to the International Statistical Classification of Diseases (ICD), before 1994 according to the 8<sup>th</sup> revision and hereafter the 10<sup>th</sup> revision.<sup>65</sup> One primary diagnosis, and when relevant, secondary diagnoses are registered with each hospital contact. The discharging physician is responsible for registration of the diagnoses.<sup>66</sup> In Study 1 and 3 the Danish National Patient Registry was used to identify incident VTE patients among 13-33 year-old Danish residents. Furthermore, this registry was in Study 1 used to ascertain VTE-provoking

factors with potential importance for mental well-being, and in Study 3 to identify patients with IDDM.

### **The Danish National Prescription Registry**

The Danish National Prescription Registry contains individual-level data on all redeemed prescriptions from Danish pharmacies since 1995, coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.<sup>67</sup> Individual-levelled information is not available for sale of over-the-counter medicine, but aggregated data is. The Danish National Prescription Registry holds an encrypted copy of the entire prescription register of the Register of Medical Products Statistics made available in 2003 for research purposes.<sup>67</sup> The Danish National Prescription Registry was used in Study 1 and Study 3 to identify psychotropic drug prescription purchases. Furthermore, this registry was in Study 3 used to ascertain antithrombotic treatment status and in the combination with the Danish National Patient Registry to identify patients with IDDM.

### **The Danish Medical Birth Registry**

The Danish Medical Birth Registry contains information on all registered births in Denmark since 1973.<sup>68</sup> This includes both live births and stillbirths (from 1973 to 2003 defined as born week  $\geq 28$  of gestation and from 2004 to present defined as born week  $\geq 22$  of gestation). Both home births and hospital births are registered.<sup>68</sup> The Danish Medical Birth Registry was used to identify recent pregnancies in Study 1.

## **4.3.2. STATISTICAL ANALYSIS**

The pseudo-value method was used to estimate risk differences of psychotropic drug prescription purchase in Study 1 and Study 3 to describe and compare long-term mental well-being. The most commonly used statistical method when using time-to-event as a primary outcome is the Cox regression model, which produces event rates as a measure of absolute risk. However, in the presence of censoring, e.g., competing risks or loss to follow-up, the event status at end of follow-up is unknown for some individuals. Such missing values imply that event rates do not translate directly into absolute risk, meaning the probability that a given person will experience an event within a stated period of time.<sup>69</sup> Risk as a measure of disease frequency has the advantage that it is readily understood from a clinical perspective. The pseudo-value method overthrows these potential pitfalls of using event rates to quantify absolute risk by replacing missing values with imputed pseudo-values.<sup>70,71</sup> Thus, the pseudo-value method reduces to simple regression on the event status indicator when there is no censoring, while at the same time handling censored observations, which allows for producing survival curves and estimating risk probabilities at a fixed point in time.<sup>70,71</sup> Thus, in Study 1



and Study 3 the pseudo-value method was used to estimate risk differences after 1 year and 5 years of follow-up.

#### 4.3.3. DEVELOPMENT OF INTERVIEW GUIDES

Informed by the results from Study 1, a two-phased data collection was applied in Study 2 to explore the essential meaning of the lived experience of adolescents and young adults following a VTE diagnosis, to gain an in-depth understating of their long-term mental well-being. The first phase was conducted to facilitate the development of interview guides for the semi-structured interviews in the second phase.

The first phase of the data collection included participant observations and informal interviews during the adolescents' and young adults' VTE admission or out-patient visit. An initial local assessment showed that in 2009 patients with VTE were admitted to 19 different hospital departments at Aalborg University Hospital alone. Thus, approaching the field involved, in addition to obtaining formal access, identification and interaction with numerous gatekeepers.<sup>72</sup> To establish the initial contact and identify relevant gatekeepers, information letters were send out (**Appendix A**) and information meetings with the healthcare professional were held at the departments. Thereby, providing the healthcare professional information on the purpose and practicalities of the research. The intent was to legitimise the research purpose among the involved health care professionals and to establish credibility both as a nurse, researcher, and a person seeking access to the field.<sup>72</sup>

With an overall attention towards mental well-being, the observations and informal interviews specifically focused on the complexities of the issues related to having VTE from the perspective of adolescents and young adults. The observations were descriptive and included grand-tour and mini-tour observations of the hospital setting, the patient, healthcare professionals, relatives, procedures, formal meetings, informal conversations, objects present, actions and events carried out, time spent, the goal trying to be accomplished and feelings expressed.<sup>73</sup> The observations lasted between 2 and 9 hours in total. In the observations the researcher took the role as participating observer and sought the position of what Hammersley and Atkinson describes an 'acceptable incompetent', open-mindedly watching, listening and asking questions.<sup>72</sup> Given the researcher did not have pervious clinical experience within the hospitals in the North Denmark Region, this did not prove difficult. However, because of the insider position as a trained nurse, special attention was paid to the risk of 'going native', thereby shifting the balance between proximity and distance.<sup>72</sup>

Field notes were gendered and included condensed accounts, representing notes taken during the actual field observations, and expanded accounts, representing recalled details written down after the actual field observations.<sup>73</sup> On the basis of the field notes interview questions were generated exemplified in **Table 2**. This included both general and specific individual questions. Thus, the questions comprising the interview guides differed in each of the individual interviews. An example of one of the interview guides is presented in **Appendix B**.

**Table 2:** Example of the development of interview questions

Participant observation, unstructured interview	General questions	Individual specific questions
<p>Patient D</p> <p>A two bed hospital room at the acute medical admission ward. The patient with DVT is sitting in the bed which is made, wearing her own clothes, waiting for the results of the ultrasound we just returned from. She explains how it had been very hard for her to judge her symptoms: "It felt like when I had the blood clot, but I didn't really know if it was enough reason for me to react on it."</p>	<p>Will you tell me, how you experience it when you feel something resembling the blood clot?</p>	
<p>Patient H</p> <p>In a corner of the hallway in the cardiac ward. The patient with PE is sitting in a chair opposite me. She explains to me how she finds it a bit strange to be hospitalised, because she doesn't feel truly ill.</p>		<p>You told me it felt strange to be hospitalised because you did not feel truly ill. Could you please elaborate on that?</p>

#### 4.3.4. INTERVIEWS

Interviews comprised the second phase of the data-collection in Study 2. Interviews was chosen as a way to encourage the participants to talk about their lives and thereby capture their lived experiences.<sup>74</sup> To ensure experiences would be related to a longer time span and not the immediate experience of having VTE the interviews took place 6-11 months after the recruitment of the participants. Nine of the interviews were conducted at the participants' home and three at the hospital, depending on the participants' preference. Involving interviewees in the organisation of the interview context may foster a more relaxed experience of the interview situation, which creates an opportunity for a deeper insight into their experiences.<sup>72</sup> Thus, in the planning of the interviews emphasis was placed on presenting several possible locations and settings for the interview.

A flexible and open approach was sought to let interviews flow in a natural way, thereby ensuring rigor in capturing the participants' perspectives by allowing them to speak freely about their lived experiences post-VTE. Thus, the questions from the interview guides were not pursued answered in a fixed

sequence but were considered prompts.<sup>72,74</sup> Thus, all interviews were opened by the question: “Please tell me about your life after you had a blood clot”, and when needed, elaborating questions were asked.

The interviews length was guided by the process of saturation to ensure depth of data.<sup>75</sup> Thus, the interviews continued until the narratives became repetitive and no new data was revealed. Interviews lasted between 45 minutes to 1 hour and 28 minutes. Interviews were digitally recorded and transcribed verbatim directly after they were conducted using the NCH Software Express Scribe Pro. The transcription resulted in 324 A4 pages.

#### 4.3.5. A PHENOMENOLOGICAL HERMENEUTICAL INTERPRETATION APPROACH

A phenomenological hermeneutical interpretation approach inspired by the French philosopher Paul Ricœur’s theory of interpretation was used in Study 2. Rather than developing a method, Ricœur presented a theory of interpretation, for which his understanding of text was fundamental. According to Ricœur,<sup>76</sup> text is any discourse fixed by writing and what is fixed is not the event, but the “said” of the speaking. Hence, the fixing of discourse frees meaning from the originating situation and the original author’s intention. Understanding is therefore not tied to the understanding of others, but to what Ricœur<sup>76</sup> describes as a proposed world of the text. A world, which the text unfolds, discovers and reveals. However, this is not disclosed to us directly, which draw the attention to one of the specific tasks of Ricœur, the grafting of the hermeneutical problem onto the phenomenological method, wherein he defines hermeneutic as: “*the theory of the operations of understanding in their relation to the interpretation of texts*”.<sup>76(p46)</sup> Thus, Ricœur<sup>77</sup> argues that textual interpretation is necessary to appropriate the meaning and the world of the text, explicating new facets of being-in-the-world. Therefore, insight into the essential meaning of adolescents and young adults lived experiences following VTE was sought through textual interpretation of the transcribed interviews thereby gaining an in-depth understanding of the long-term mental well-being.

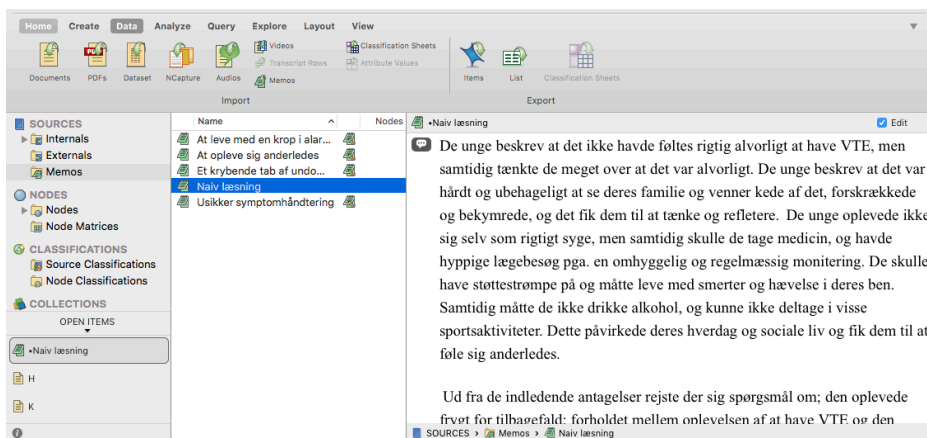
According to Ricœur’s understanding a text is: *a movement from sense to reference, from what the text says to what it speaks about*.<sup>76(p218)</sup> Thus, interpretation constitutes a movement from the immanent pattern of the text to the meaning of the text, reaching a comprehensive understanding. A meaning of the text not understood as an intention hidden behind the text but a world unfolded in front of it opened up by the depth semantics of the text.<sup>78</sup> In the light of this Ricœur proposes to describe interpretation as a dialect movement between explanation and understanding, moving from understanding to explaining and from explanation to comprehension.<sup>76</sup> Thus, explaining and understanding are not considered contradicting, but instead considered complementary and reciprocal. The analysis of the interview text

thereby consisted of three levels; a naïve reading; a structural analysis and; a critical analysis and discussion.<sup>76,77,79</sup> The structural analysis served as a mediator between the surface interpretation and the depth interpretation.<sup>76</sup> In the three interpretation levels the analysis moved dialectically between understanding, explanation and comprehension, between the parts and the whole and the whole and the parts, in what Ricœur speaks of as an endless hermeneutical spiral.<sup>76,79</sup>

To facilitate the analysis of the transcribed interviews, it was performed in the qualitative data analysis software, NVivo (QSR International v.10).<sup>80</sup> This allowed a constant movement between the whole and the parts and between the three levels of analysis. To give an open and transparent presentation of the analytical process an example of how the naïve reading, the structural analysis, and the critical analysis were performed in NVivo is presented in the following elaboration of the analytical levels.

### Naïve reading

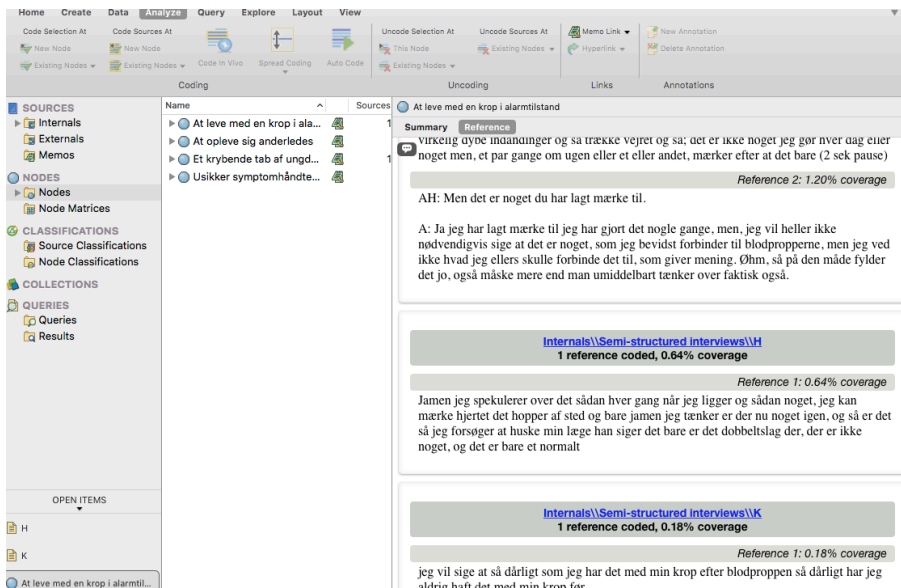
The naïve reading was the initial spontaneous impression of the interview text as a whole. In NVivo, all transcribed interviews were imported as documents and read one by one in order to acquire a general sense of the whole, by being open towards the text and making guesses and presumptions **Picture 1**. A Memo was created labelled Naïve reading where the guesses and presumptions were recorded. Collectively these comprised the naïve analysis text, the immediate understanding of the meaning, which raised questions to be pursued in the following stages of analysis.



**Picture 1.** Naïve reading in NVivo

## Structural analysis

In the structural analysis the interview text was read again and divided into text structures coded in NVivo notes according to what was said in the interview text (quotations) related to the questions raised in the naïve reading **Picture 2**. The analysis continued forward and backwards between the whole and the parts in a hermeneutical way, thereby extracting the meaningful content and patterns in the text. Inspired by Dreyer et al.'s<sup>79</sup> description, short stories were created grasping what the text spoke about across all interviews. This builds on Ricœur's<sup>79</sup> notion of objectifying a text instead of subjectifying it to enable a comprehensive understanding that moves beyond the authors' intention towards a deeper understanding of what the text refers to. Thus, distinction was created in the interpretation and the text structure by creating short stories grasping what the interview text spoke about across the data. As such, nothing was added the meaning and the examples originated in the quotes. The short stories were created using the NVivo function Memo Links, and recorded in Memos. Finally, four themes were identified and structured relating to both the NVivo notes and the short stories.

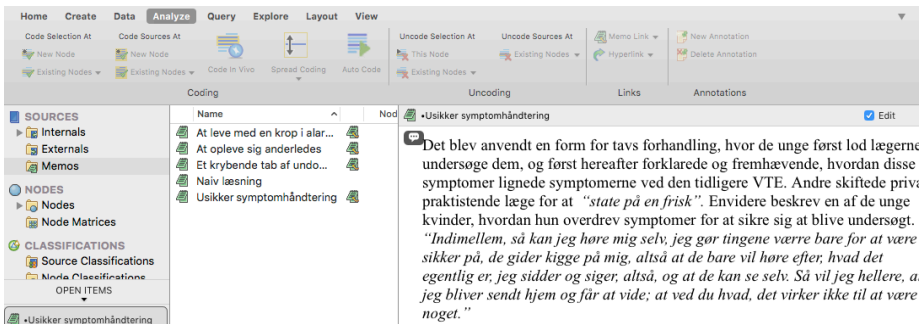


**Picture 2.** Structural analysis in NVivo

## Critical analysis and discussion

The themes identified in the structural analysis were critically interpreted in relation to both the short stories and the quotations. Linked Memos were created enabling the dialectic movement between explanation and comprehension unfolding the meaning of the text **Picture 3**. One of the most significant

ideas in Ricœur's thinking is the phenomenological hermeneutical approach as an argumentative discipline. According to Ricœur there is always more than one way of constructing a text. An interpretation must therefore, not only be probable, but more probable than another interpretation, and it is the argument that gives credibility and validity to the interpretation.<sup>77</sup> Thus, on the basis of relevant theoretical and empirical literature, the themes were discussed in order to argue in favour of a credible and valid interpretation. For this, NVivo was not used.



Picture 3. Critical analysis in NVivo

### Comprehensive understanding

On the basis of the critical analysis and discussion a comprehensive understanding was reached. This constituted what Ricœur refers to as the final act of understanding: *"the appropriation of the meaning of the text."*<sup>77(p141)</sup>. Thus, the comprehensive understanding was the appropriation of the essential meaning of adolescents and young adults lived experiences following VTE and constituted an in-depth understanding of their mental well-being.

## 4.4. ETHICAL CONSIDERATIONS

To conduct research involving young patients with an overall focus on mental well-being led to careful ethical considerations, as the participants would possibly belong to two groups considered particularly vulnerable.<sup>81</sup> Thereby, increasing the possibility of exploitation.<sup>82</sup>

The North Denmark Region Committee on Health Research Ethics assessed the study and in accordance with Danish law a formal ethics approval was not required. The study complies with existing rules on data storage, the ethical guidelines for nursing research in the Nordic countries,<sup>83</sup> and the Danish Health Act.<sup>84</sup> Authorisation by the Danish Data Protection Agency was

obtained (Study 1 and 3; File No. 2012-41-0633, Study 2; File No. 2012-41-1134).

All participants in Study 2 received information orally and in writing about the nature and purpose of the study (**Appendix C**). Informed consent was obtained before enrolment, and the participants retained the right to withdraw from the study at any time, which was underlined. One of the participants was under the age of 18 at the time of recruitment, thus informed consent was obtained from the participant and the holder of custody was informed hereof.<sup>84</sup> Anonymity and confidentiality were ensured by anonymising names and handling data as confidential material. Thus, the interview recordings and transcriptions were stored with pass-word protection.

Research involving interviews are widely considered minimal risk, although this method may cause considerable emotional distress.<sup>74</sup> Thus, the ethical requirements incite the researcher to reflect on the transformative power of the encounter, when participants are asked to put their experience of suffering and vulnerability into words.<sup>85</sup> To explore the participants lived experience focused on mental well-being posed a possible exposure of suffering and vulnerability. Thus, the interview situation was encountered with sensitivity and awareness. If the participants became emotionally affected a break was offered and permission was sought from the participant before continuing. At the end of the interview the participants were given my contact information, and were encouraged to contact me if they had any questions, concerns, or required further information about the study.

## CHAPTER 5. RESULTS

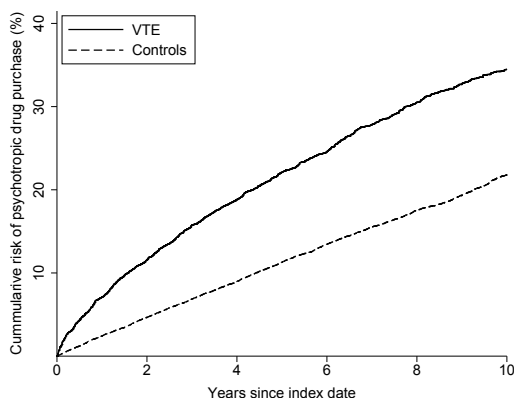
In the following the results and findings of Study 1, Study 2, and Study 3 are summarised. These sections are followed by an integrated mixed methods interpretation of the three studies.

### 5.1. STUDY 1: DESCRIPTION OF LONG-TERM MENTAL WELL-BEING OF ADOLESCENTS OR YOUNG ADULTS DIAGNOSED WITH VTE

The following presentation of results is based on Study 1: *“Use of psychotropic drugs following venous thromboembolism in youth A nationwide cohort study”*.<sup>86</sup>

For the description of long-term mental well-being using psychotropic drug purchase as a proxy, 5027 patients with an incident diagnosis of VTE between the ages of 13-33 were identified. Of these, 14 died on the day of diagnosis and 881 had a psychotropic drug prescription purchase within 2 years prior to the diagnosis, and were therefore excluded. Among the 20,661 sex and age matched controls, 1,368 had a psychotropic drug prescription purchase within the last two years and were excluded. Thus, the study population comprised 4,132 VTE patients and 19,292 age and sex matched controls. Of the VTE patients almost two thirds were women and the mean age was 25 years. Compared with the age and sex matched controls, VTE patients had more recent pregnancies (17.5 % vs 11.6 %) and history of other known VTE-provoking factors with potential importance for mental well-being (16.5 % vs. 1.6 %). VTE-provoking factors included; diagnosis of cancer, rheumatoid arthritis, inflammatory bowel disease within 1 year of index date; trauma requiring hospital admission within 3 months of index date and; surgery requiring one or more days of hospital admission within the last 3 months of index date.

As depicted in **Figure 2**, patients with VTE were found to have a substantially higher risk of a psychotropic drug purchase than the sex and age matched controls during a follow up period of up to 10 years.



**Figure 2:** Kaplan-Meier estimates of the risk of psychotropic drug purchase as a function of time.



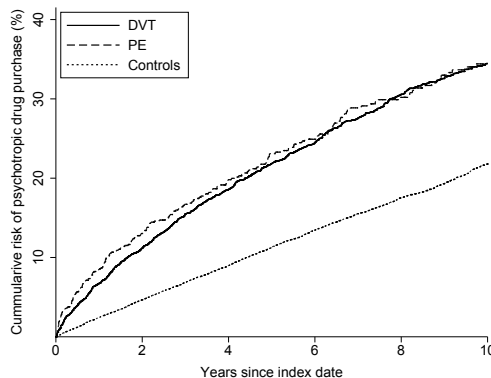
Significant risk differences of 4.7 % [95 % confidence interval (CI): 3.9,5.5] after one year and 10.8 % [95 % CI: 9.4,12.3] after 5 years were found. The higher risk of psychotropic drug purchase persisted when taking into account recent pregnancy or VTE provocation (1-year risk difference 4.1% [95% CI: 3.5,5.1], 5 year risk difference 9.6% [95% CI: 8.3,11.2]). Similar risk differences were found across age strata (age  $\leq 25$  years and age  $>25$  years) and period of index date (1997–2002 and 2003–2010).

## Sex

Male and female VTE patients were observed to have similar absolute risks of psychotropic drug purchase. In contrast, the absolute risk of psychotropic drug purchase was higher for females than males among the sex and age matched controls. Thus, the stratified analysis showed the risk difference between male VTE cases and controls was significantly higher than the risk difference between female VTE cases and controls after 5 years of follow-up (risk difference males versus females: 4.1 [95 % CI: 1.0,7.2]).

## VTE type

During the 10-year follow-up period, the risk of a psychotropic drug purchase was similar among patients with PE and patients with DVT depicted in **Figure 3**.



**Figure 3:** Kaplan-Meier estimates of the risk of psychotropic drug purchase as a function of time according to VTE status.

## Distribution of psychotropic drug classes

No marked difference in the distribution of purchase according to drug class was found between the VTE patients and the sex and age matched controls. The most frequently purchased drug was antidepressants (53 %) followed by sedatives (22%), anxiolytics (20 %), and antipsychotics (5%). When conducting sensitivity analyses using these difference agents as individual outcomes, similar patterns of psychotropic drug purchases were found as in the main analysis.

## 5.2. STUDY 2: EXPLORATION OF THE ESSENTIAL MEANING OF ADOLESCENTS AND YOUNG ADULTS LIVED EXPERIENCES FOLLOWING VTE

The following presents a summary of the findings of Study 2: *“Adolescents’ and young adults’ lived experiences following venous thromboembolism. “It will always lie in wait”*. The summary of findings is driven from the 3 analytical levels and is presented according to the four identified themes and a comprehensive understanding.

### A creeping loss of youth immortality

The theme *A creeping loss of youth immortality* was critically interpreted in relation to the short story and excerpts from the interview text (quotations) presented in **Table 3**. It showed how the sense of immortality had progressively been shattered and mortality had become salient in life after VTE. This was not an immediate revelation, but a realisation in the confrontation with the reaction of others, especially parents’ reactions. Thus, the reactions of others were important for the perception of having VTE. The initial experience of VTE was characterised as uncritical also by participants who had experienced a near fatal PE. However, when confronted with the reaction of others, rumination on what happened and could have happened was initiated. Thus, a creeping loss of youth immortality was initiated and mortality became salient. This caused psychological distress and for some, resulted in late reactions of anxiety and nightmares. Furthermore, the salience of mortality made it important to live life to the fullest, described as an obligation to accomplish something in life.

**Table 3** Short story and quotations

A creeping loss of youth immortality	
Short story	<p><b>Sh** it was a close call</b></p> <p>Getting a blood clot is a serious thing, but at the time I had the blood clots, it actually didn't feel like it, because it was too unreal. I didn't feel as bad as I properly was. What scared me the most was actually to see my parents' reaction. When they talk about it, they almost cry – I think that is the really scary part, that it can make my father cry; then I know it was critical back then, and then you kind of realise: “sh** it was a close call”. It is not until now, afterwards, I am beginning to realise that it was a blood clot and not just something flu-like I had. It actually was truly critical, and it can stay with you. You become aware of how nothing lasts forever, and it is kind of a wake-up call. - Stop, think about what you are doing and who you are.</p>
	<p><i>“I have become aware of how little it takes”</i></p> <p><i>“Nothing lasts forever”</i></p> <p><i>“My mother told me, my face turned blue, and could see how my body desperately needed oxygen, and this really frightened them. I don't remember it being that bad, but now afterwards, when you think about it, well, it scares me, because it was probably a closer call than I just thought.”</i></p> <p><i>“It was really, really tough; I am not used to seeing my father cry. He has always been one tough cookie. He never cries. It was very scary to experience.”</i></p> <p><i>“I was scared sh**less and had nightmares, dreamt I burned alive. Well, at that point all the emotional stuff began to emerge, that I actually could have died.”</i></p> <p><i>“It is and ongoing fight”</i></p>

The perception of being different

The theme *The perception of being different* was critically interpreted in relation to the short story and excerpts from the interview text (quotations) presented in **Table 4**. It showed how a perception of being different was prominent in life after VTE, and a cause of distress. The participants did not consider themselves chronically ill, but everyday life was affected. Management of anticoagulant treatment, compression stockings, the perception of being at lifelong risk of recurrence, and physical symptoms related to post thrombotic syndrome restricted the ability to feel normal. Hence, in spite of a strive for normalisation, some of the participants described how they felt they had become a different person mentally and physically. The perception of being different was widely apparent in social contexts among the participants requiring anticoagulant treatment. Alcohol consumption was considered a central part of social life and alcohol restrictions related to the anticoagulant treatment was subject to a feeling of exclusion. In addition to feeling different from peers, the participants also described feeling different from other VTE patients, as they recognised VTE as a disease occurring in old age. This double perception of difference induced a feeling of loneliness, even though the participants emphasised how caring and supportive their relatives were. To meet another young VTE patient was, by the few participants who had by chance done so, described as reassuring and moderated the feeling of being different.

Table 4 Short story and quotations

The perception of being different	
	<b>I am not like the others anymore</b>
Short story	After the blood clot, I suddenly felt different. I wasn't like the others anymore. For instance, I can't drink alcohol because of the medicine I take. And that makes me feel excluded from certain things, and stops me from really being part of the group. Then you don't really feel normal. I also have to wear a compression stocking; you feel a little weird when you have to wear that darn compression stocking. It's embarrassing, especially during the summer and at PE. I can see people think: "That is quite strange". You know, people don't really understand it, and do not get how it is, and what it is. Of course, they listen when I speak, but I don't really feel understood. A blood clot is something an old lady has, and it makes you reflect. - You are bit of a loner. Then it is super nice to meet somebody who has experienced some of the same, because we understand each other and relate to each other and share experiences.
	<i>"Suddenly I felt different than the others, I think that was hardest, that I suddenly wasn't like the others anymore."</i>
Quotations	<i>"You just feel a little left out when you can't participate; when you can't get drunk and be happy in the company of the others, then the party becomes different for you, you're a part of it, but not in the same way."</i>
	<i>"Most people say that it's really not what you would expect a girl of your age to go through, and that's what I think as well. I just got one of the pamphlets again, and all the pictures in it are of somebody walking with a crutch or a walker [...] it makes you think, you are a bit like a loner."</i>
	<i>"I actually feel alone, I know it sounds stupid in a way, I have a nice boyfriend and family, it is just so hard to explain; it's just, they listen and stuff, but I don't really feel understood."</i>
	<i>"It is reassuring in some way that you are not alone in having experienced this, that somebody else has experienced it and can relate to it."</i>

### To live with a body in a state of alert

The theme *To live with a body in a state of alert* was critically interpreted in relation to the short story and excerpts from the interview text (quotations) presented in **Table 5**. It showed that fear of recurrence was a great concern in life after VTE, and the uncertainty of if, when and what would happen entailed heightened body awareness. The participants described being highly alert of signs and symptoms of VTE and found it essential to be able to recognise these. The body was perceived as a weak link and as having a flaw. Thus, the risk of recurrence was experienced as something persisting, as something that would follow them through life and regardless of type or severity of VTE ambiguous symptoms caused anxiety and psychological distress, as mortality was highly salient. The feeling of uncertainty enhanced and resurfaced in situations of increased risk of recurrence. Thus, a pregnancy expected to be a positive experience, became a course of illness as it made the risk of thrombosis highly apparent. To relieve uncertainty, it was essential to have a clear identified cause for the VTE and to be well-medicated. However, the feeling of uncertainty was also present among participants well-medicated, and participants with a clear identified cause. They expressed how being well-medicated did not relieve the feeling of uncertainty completely, and how they were aware that they in certain circumstances always would be at higher risk of recurrence. Thus, to be highly alert of signs and symptoms were perceived important among all participants as the VTE would always lie in wait.

**Table 5** Short story and Quotations

To live with a body in a state of alert	
Short story	<p><b>It is always looming in the background</b></p> <p>The blood clot really fills up in my brain, it is hard to explain why, but in a way it is always there, lurking. I have to take medicine every day, and my leg swells a lot, so it's in some way always present. Every day it is a part of my life. There are also a lot of thoughts; is it going to affect me again? Is it something I will pass on to my children? And what will happen if I get pregnant? I have often thought: "I am not ill", and "I am like everybody else" But you're not, because you will always have to bear in mind that it can happen again. Sometime, I feel like it will definitely happen again. I know I have been told it shouldn't happen when I take my medicine, but I still feel like – One thing is what they say; another thing is what will happen next time? I have accepted that my body has a flaw, that I am the weak link now. I have become more aware of what happens in my body, what it complains about, and I notice more things now than I did before. When I lie down in bed, I get this sensation and I ruminate. In that way, it makes itself present in a stronger way than you think it would.</p>
	<p><i>"This will stick with me for the rest of my life, like a little cloud that floats in your mind, that is how it is."</i></p> <p><i>"I have become more alert than I used to. I can feel more things now, than I could previously. You take it for granted, how your body works. You don't think about it. Now I do. I feel everything in my body now. I have to be more alert of what my body does, what it complains about, so I can be more observant next time."</i></p> <p><i>"If I am in pain and can't understand what is wrong, it really makes me cry, and actually I would say that the physical pain during this has not been the worst, it is the mental pain that came after that was the worst."</i></p> <p><i>"I could feel how it kicked me right back into it; I found it to be really, really tough."</i></p> <p><i>"If you don't know where it came from you cannot know whether it will come back again."</i></p> <p><i>"Even though I was told, that it can't happen again as long as I take my medicine, it's still just not enough. It is the anxiety I think, the fear that this could happen again."</i></p>

Symptom management insecurity

The theme *Symptom management insecurity* was critically interpreted in relation to the short story and excerpts from the interview text (quotations) presented in **Table 6**. It showed how worry and concern that symptoms suggestive of VTE recurrence would be neglected was prominent in life after VTE. This was enhanced by a delay in the initial diagnosis, which resulted in a breach of trust in doctors and the doctors’ ability to correctly interpret future symptoms of VTE. Thus, to be persistent and in control of own health was considered vital. Self-managed anticoagulant treatment was described as a possibility to be in control. However, when experiencing symptoms suggestive of VTE recurrence the ability to be in control was described as limited. In this case, they had to rely on the health care system and the doctors’ assessment to confirm or refute their suspicion. Consequently, different strategies would be used to ensure VTE recurrence would be recognised. The participants would go to great lengths to ensure concerns would be taken serious because they feared VTE recurrence would be fatal. Consequently, the participants described frequent doctors’ visits and hospital readmissions, because of symptom management insecurity.

Table 6 Short story and Quotations

Symptom management insecurity	
Short story	<p><b>I could actually have died of this!</b></p> <p>I saw my GP and the on-call GP several times before they found out it was a blood clot. And you can feel a bit annoyed they didn't do more. I could actually have died of this. I lost a lot of confidence in the doctors. It helped a bit when shortly after having the clot my GP explained to me how hard it actually can be to detect it. But when you have been through this, you know you have to trust yourself and not always trust doctors blindly. Sometimes you have to put your foot down and tell them, <i>"Well this is how I feel"</i> because I want people to take me serious when it is something related to the blood clot. Sometimes I can hear myself make matters worse to be sure they will check my out. It is tough, because it is all up to the doctor; does he send me home or send me on? I'd rather be admitted and checked out when I feel something, because there may as well be something as there may not be. There must have been 5-6 times where they found nothing.</p>
	<p><i>"It was so disturbing how three doctors, as well as my GP more than once, could disregard my signals, I didn't feel I could trust any doctors, and I still don't."</i></p> <p><i>"Suddenly it has become super important to me, that everything is under control, and I am best in control if I control it myself. The control in knowing, that I know what it is all about."</i></p> <p><i>"To make a fresh start."</i></p> <p><i>"Sometimes I can hear myself make matters worse, just to make sure they will take a look at me, and to make sure they will listen to me and to what I am telling them. I'd rather they have a look at me and then be sent home with the message that everything seems fine."</i></p> <p><i>"I rather they find out nothing is wrong, than something shows up. I would rather be admitted 40 times in one year."</i></p>

### **Comprehensive understanding**

On the basis of the critical analysis and discussion the following comprehensive understanding of the essential meaning of adolescents and young adults lived experiences following VTE was reached constituting an in-depth understanding of the long-term mental well-being.

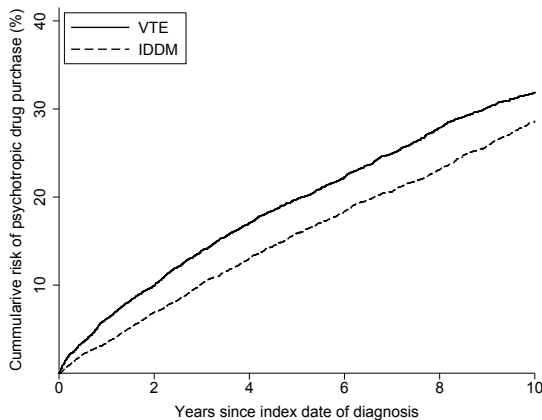
Mortality is salient in life following VTE in adolescence or young adulthood, and especially parents' reactions seem important for the sense of loss immortality. As such, parents play an important role in the illness perception and adaption. The fear of recurrence points back to the initial VTE event but manifests particularly in fear of recurrence, which is an important source of psychological distress. Fear of recurrence persists over time, and the concomitant uncertainty, an uncertainty in which mortality manifests, entails a heightened body awareness. Thus, the body is in a state of alert. To relieve uncertainty, it is important to find a cause for the VTE and be well-medicated. However, the feeling of uncertainty is never completely relieved as it is recognised that in certain circumstances they will always be of higher risk of recurrence. Thus the VTE is described as something that will always lie in wait. Following a diagnosis of VTE a perception of being different both as a VTE patient and among peers is prominent, which results in a feeling of loneliness. Meeting another VTE patient is experienced as reassuring and moderates this perception, thus peers support could play an important role in helping foster healthy mental well-being. Furthermore, a pronounced insecurity regarding symptom management is evident in life after VTE, amplified by a delay in the initial diagnosis, and concomitant loss of confidence in health care professionals. Thus to be in control is perceived vital and when experiencing symptoms of VTE different strategies are used to ensure symptoms suggestive of VTE will be recognised, consequently an over-utilisation of healthcare services is described.

### 5.3. STUDY 3: COMPARISON OF LONG-TERM MENTAL WELL-BEING FOLLOWING VTE VERSUS IDDM IN ADOLESCENTS AND YOUNG ADULTHOOD

The following presents the results of study 3: *Psychotropic drug usage following venous thromboembolism versus diabetes mellitus in adolescence or young adulthood: A Danish nationwide cohort study.*

For the comparison of long-term mental well-being, using psychotropic drug purchase as a proxy, 5,573 patients with VTE and 5,761 patients with IDDM were identified. Of these, 18 patients with VTE had died on the day of diagnosis, and 1,003 of patients with VTE and 572 patients with IDDM had a psychotropic drug purchase within two years prior to diagnosis. Thus, the study population comprised 4,551 VTE patients and 5,181 IDDM patients. Compared to the IDDM patients VTE patients were more often female (68.0% vs. 48.9%), and were slightly older (mean age 25.6 years vs. 23.1 years).

Patients with VTE were observed to have a higher risk of psychotropic drug purchase compared to patients with IDDM during the follow-up period of 10 years (**Figure 4**).



**Figure 4:** Kaplan-Meier estimates of the risk of psychotropic drug purchase as a function of time.

A significant risk differences of 2.7% [95 % CI: 1.8,3.6] was found after 1 year of follow-up. Absolute risk of psychotropic drug purchase increased in a comparable manner for VTE and IDDM patients, during follow-up, exhibiting 5-year risk difference of 3.8 % [95 % CI: 2.2,5.5]. Repeating the risk difference calculations for each psychotropic drug class (antidepressants, sedatives, anxiolytics, antipsychotics) did not materially change the overall findings.

Risk differences persisted across age strata. Among both VTE and IDDM patients, absolute risks were found higher in the older age groups. Male and female VTE patients were observed to have similar absolute risks, whereas absolute risks were higher for female than male IDDM patients, resulting in a higher risk difference between male than females after 5 years of follow-up.

### Anticoagulant-treatment status

In an attempt to study whether mental well-being would differ among long-term users and non-users of anticoagulation, an analysis was constructed with time zero starting after one year, including only patients with no history of a claimed prescription for a psychotropic drug within the first year after the VTE diagnosis. At one year after diagnosis, 654 of the VTE patients had a retrieved prescription of coumarin within 60 days and no psychotropic drug purchase. VTE patients non-anticoagulated at 1 year were observed to have a higher risk of psychotropic drug purchase compared to IDDM patients, whereas similar risks were observed between the anticoagulated VTE patients and the IDDM patients (**Table 7**).

	Risk difference (%): VTE vs. IDDM (95% CI)
All	1.7 (-0.0 - 3.5)
Anticoagulated	-0.1 (-3.7 - 2.5)
Not anticoagulated	2.2 (0.4 - 4.1)

Number of participants contributing data (VTE: anticoagulated 654, not anticoagulated 3,188; IDDM 4,697)

**Table 7.** Risk differences of psychotropic drug purchase by diagnosis (VTE, IDDM) 5 years after initial diagnosis, stratified according to anticoagulant treatment status at 1 year for the VTE group.



## 5.4. INTEGRATED MIXED METHODS INTERPERTATION

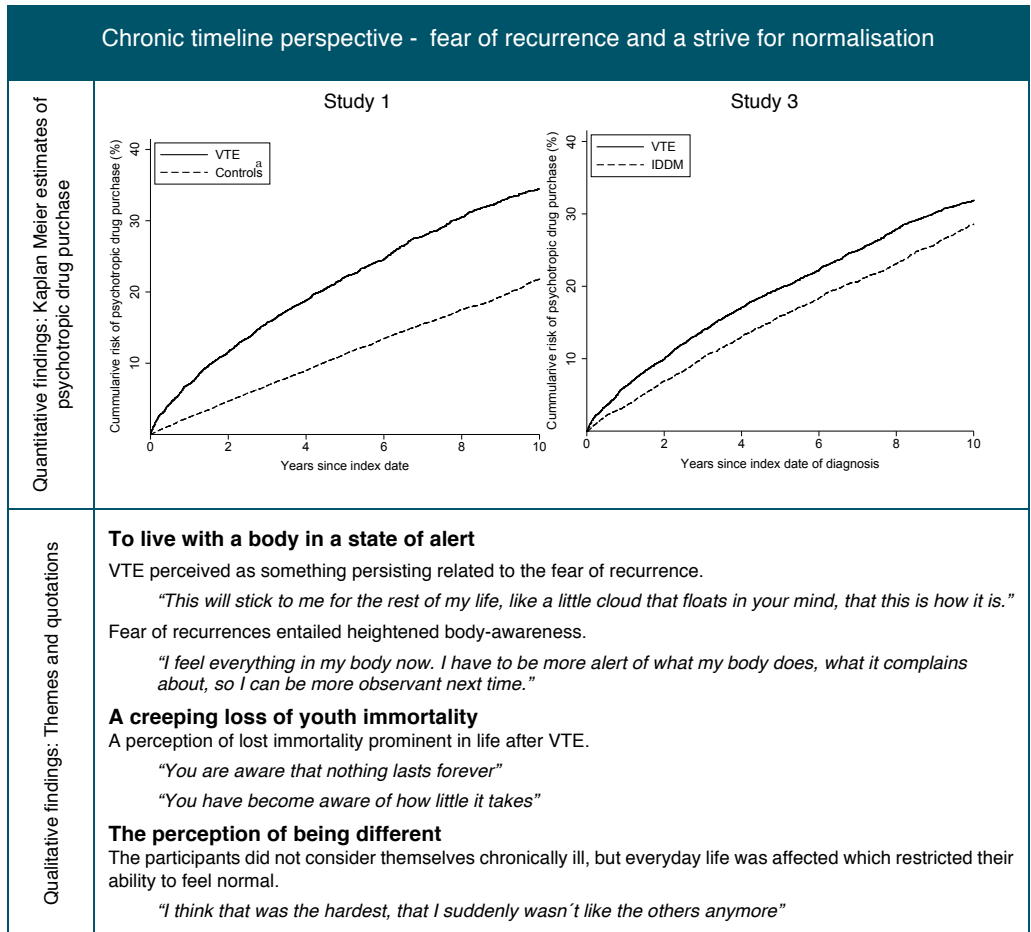
The integrated mixed methods interpretation of the quantitative and qualitative findings from Study 1, 2, and 3 is presented in the following mixed methods joint displays and narrative weaving descriptions and inspired by the notion of *confirmation*, *expansion* and *discordance*. Through the combination of description (Study 1), exploration (Study 2), and comparison (Study 3) the following integrated themes were identified 1) Chronic timeline perspective – fear of recurrence and a strive for normalisation 2) Navigating uncertainty, and 3) Perceived health threat versus illness severity.

### 5.4.1. CHRONIC TIMELINE PERSPECTIVE - FEAR OF RECURRENCE AND A STRIVE FOR NORMALISATION

#### Narrative weaving

A perspective of a chronic timeline appeared when describing the mental well-being among patients with VTE using subsequent psychotropic drug purchase as a proxy. The young patients with VTE were observed to have a substantially higher risk of psychotropic drug purchase than sex and age matched controls over time. The exploration of adolescents and young adults' lived experience following VTE *confirmed* this finding. VTE was perceived as something persisting and caused psychological distress. The exploration also *expanded* the insights into the chronic timeline perspective. The chronic timeline was widely connected to the fear of recurrence and the concomitant incessant uncertainty, an uncertainty in which mortality manifested and entailed a heightened body awareness. Thus, the feeling of immortality was lost and replaced by a salient feeling of mortality. This was based on the initial VTE but showed in the uncertainty of recurrence and a body highly alert of signs and symptoms, causing anxiety and psychological distress. In addition to the fear of recurrence the integrated theme of a chronic timeline perspective also showed in the impact on everyday life. Management of anticoagulant treatment, compression stockings and physical symptoms related to the post thrombotic syndrome restricted the ability to feel normal. The comparison of long-term mental well-being of adolescents and young adults with VTE versus chronically ill young patients with IDDM *confirmed* the chronic time line perspective. Patients with VTE were observed to have a significantly higher risk of psychotropic drug purchase in the long-term when compared to patients with IDDM. However, in *discordance* herewith, the exploration showed that the patients perceived the VTE as something persisting but did not necessarily consider themselves being chronically ill. Everyday life was affected and a feeling of being different both among peers and as a VTE patient was prominent, which introduced another dimension to the restricted ability to feel normal. This was perceived particularly challenging as they strived for normalisation.

## Joint display

<sup>a</sup> Population controls matched on sex and birth year.

## 5.4.2. NAVIGATING UNCERTAINTY

### Narrative weaving

To navigate uncertainty was found central for the long-term mental well-being. In the exploration of adolescents and young adults' lived experience following VTE, the level of uncertainty depended on whether the VTE was provoked or unprovoked. It was described to be essential to know where the VTE came from in order to know whether it would come back. Thus, to find a cause for the VTE was linked to the chance of determining risk of recurrence, and not having a cause was thereby related to greater uncertainty and concomitant psychological distress. This poses a possible *expansion* for the findings of higher risk difference of psychotropic drug purchases among men than among women in the description of long-term mental well-being, as young men less often have an obvious precipitating factor for their VTE compared with young women. In the exploration, the integrated theme of navigating uncertainty also presented itself in relation to anticoagulant treatment. Anticoagulant treatment was perceived as a protective factor of paramount importance for preventing recurrence. Thus, anticoagulant treatment represented a key aspect in relieving uncertainty of recurrence along with concomitant psychological distress. The comparison of long-term mental well-being *confirmed* the possible role of anticoagulant treatment for long-term mental well-being. Compared to young patients with diabetes, a higher risk of psychotropic drug purchase was observed among patients with VTE not anticoagulated after 1 year whereas the risk was comparable for patients receiving anticoagulant treatment after 1 year. However, *expanding* on this, the exploration showed how anticoagulation therapy did not relieve uncertainty completely. Especially in saturations of increased risk, uncertainty resurfaced and was often enhanced. Thus, a pregnancy, which was expected to be a positive experience, made the risk of thrombosis highly apparent, which contributed to greater uncertainty. Furthermore, the exploration showed how the navigation of uncertainty was complicated by delay in the initial diagnosis of VTE. The delay resulted in a breach of trust in doctors' ability to correctly interpret future symptoms of VTE. This enhanced the uncertainty and made it vital to be in control. Thus, to navigate uncertainty, when the ability to be in control was limited, different strategies were used to ensure VTE recurrence would be recognised, including a form of salient negotiation and exaggeration of symptoms. Consequently, this resulted in many visits to the general practitioner as well as hospital admissions.

## Joint display

Navigating Uncertainty																		
Quantitative findings: Risk differences of psychotropic drug purchase within 5 years after diagnosis	<div>Study 1</div> <table><tr><th colspan="2">Risk difference (%): VTE vs. controls<sup>a</sup> (95% CI)</th></tr><tr><td>All</td><td>10.8 (9.4,12.3)</td></tr><tr><td>Male</td><td>13.7 (11.1,16.3)</td></tr><tr><td>Female</td><td>9.6 (7.8,11.3)</td></tr></table>	Risk difference (%): VTE vs. controls <sup>a</sup> (95% CI)		All	10.8 (9.4,12.3)	Male	13.7 (11.1,16.3)	Female	9.6 (7.8,11.3)	<div>Study 3</div> <table><tr><th colspan="2">Risk difference (%): VTE vs. IDDM (95% CI)</th></tr><tr><td>All</td><td>1.7 (-0.0 - 3.5)</td></tr><tr><td>Anticoagulated</td><td>-0.1 (-3.7 – 2.5)</td></tr><tr><td>Not anticoagulated</td><td>2.2 (0.4 - 4.1)</td></tr></table>	Risk difference (%): VTE vs. IDDM (95% CI)		All	1.7 (-0.0 - 3.5)	Anticoagulated	-0.1 (-3.7 – 2.5)	Not anticoagulated	2.2 (0.4 - 4.1)
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Anticoagulated	-0.1 (-3.7 – 2.5)																	
Not anticoagulated	2.2 (0.4 - 4.1)																	
Qualitative findings: Themes and quotations	<div>To live with a body in a state of alert</div> <p>To relive uncertainty of recurrence it was essential to find a course for the VTE.</p> <p><i>"If you don't know where it came from you cannot know whether it will come back again."</i></p> <p>It was important to be well-medicated. However, this did not relive the feeling of uncertainty completely.</p> <p><i>"Even though I was told that it can't happen again as long as I take my medicine, it's still just not enough. It is the anxiety, I think, the fear of knowing this could happen again."</i></p> <p>Feeling of uncertainty enhanced and resurfaced in situations of increased risk.</p> <p><i>"I could feel how it [pregnancy] kicked me right back into it; I found it to be really really tough."</i></p> <div>Symptom management insecurity</div> <p>Initial delay in diagnosis enhanced uncertainty and made control vital.</p> <p><i>"Suddenly it has become super important to me, that everything is under control, and I am best in control if I control it myself. The control in knowing, that I know what it is all about."</i></p> <p>Different strategies were used to ensure VTE recurrence would be recognised.</p> <p><i>"Sometimes I can hear myself make matters worse, just to make sure they will take a look at me, and to make sure they will listen to me and to what I am telling them."</i></p>																	

<sup>a</sup> Population controls matched on sex and birth year.

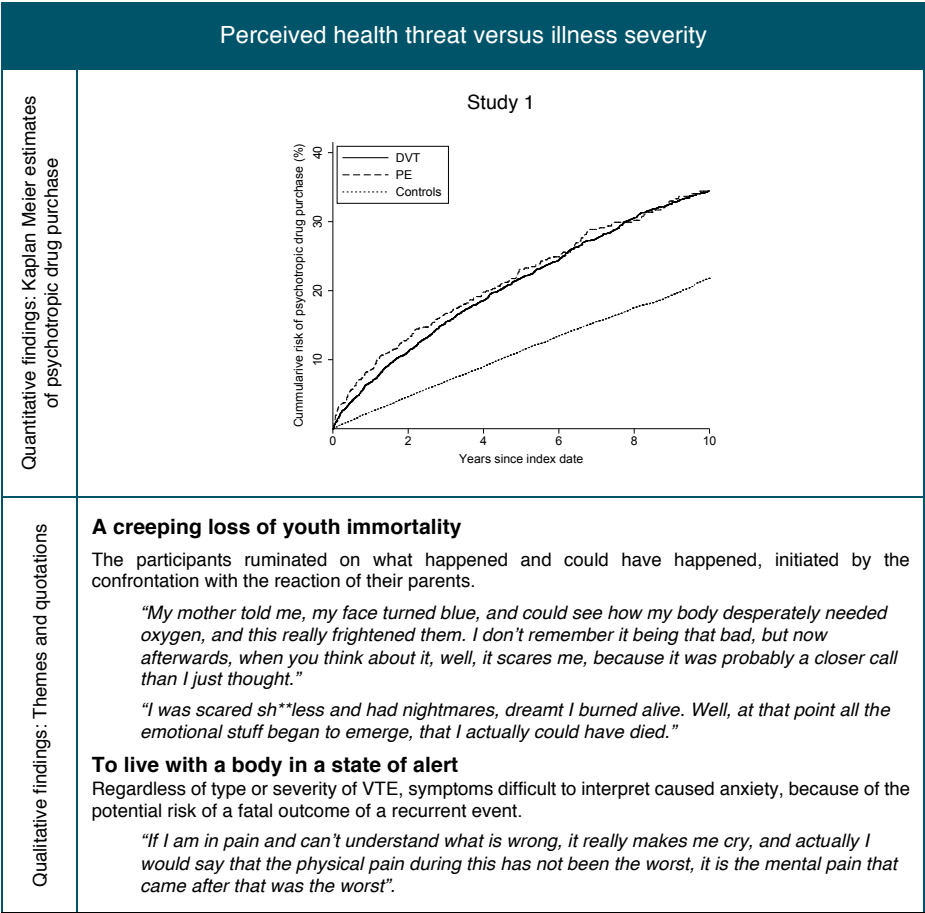
## 5.4.3. PERCEIVED HEALTH THREAT VERSUS ILLNESS SEVERITY

## Narrative weaving

Illness severity was found to play a less significant role than perceived health threat for the long-term mental well-being. The description of long-term mental well-being showed similar increased risks of psychotropic drug purchase among patients with DVT and patients with PE. The exploration of the essential meaning of adolescence and young adults lived experience following VTE *expanded* this finding. The initial experience of VTE was characterised as uncritical, also by patients who had experienced a near fatal pulmonary embolism. However, retrospectively the participants came to think and reflect on what happened and could have happened, often initiated by confrontation with the reaction of their parents. The potential life-threatening aspect of the disease became a pivotal point. The potential life-threat pointed

both back to the initial VTE, but also forward to the perception of future health-threat and potential risk of dying of a recurrent event. Thus, the retrospective appraisal of health threat and perception of future health threat was found more important than actual illness severity.

Joint display



<sup>a</sup> Population controls matched on sex and birth year.

## CHAPTER 6. DISCUSSION

In this section, the findings from the integrated mixed methods interpretation are discussed, structured according to the three identified themes. This is followed by methodological considerations including discussion of the mixed methods research process, design and methods of the sub-studies, and the generalisability and transferability of the results.

### 6.1. DISCUSSION OF FINDINGS

The long-term mental well-being of adolescents and young adults diagnosed with VTE, involved three integrated themes 1) Chronic timeline perspective - fear of recurrence and a strive for normalisation 2) To navigate uncertainty and 3) Perceived health threat versus illness severity.

#### **Chronic timeline perspective - fear of recurrence and a strive for normalisation**

The results showed a chronic timeline in regards to mental well-being with an increased risk of psychotropic drug purchase and psychological distress persisting over time. These results support previous research where longer time span since VTE have not shown to be associated with less anxiety and depression or better mental QOL.<sup>5-7,20,46,48</sup> Thus, indicating the psychological impact of VTE does not obliterate over time. The persisting impairment of mental well-being was largely connected to the fear of recurrence and concomitant uncertainty in which mortality had manifested and entailed heightened body awareness. The patients experienced what Koocher and O'Malley<sup>87</sup> in the early 1980's described as "The Damocles Syndrome". The patients were glad to be alive after the VTE, but now had to live with the risk of recurrence and death. Interestingly, this mirrors findings in young cancer survivors where uncertainty and lack of control related to fear of recurrence have been identified as an important cause of impaired functioning, psychological distress and lower QoL.<sup>88,89</sup> An uncertainty persisting in long-term with one third of young testicular cancer survivors still exercising fear of recurrence 12 years after ended treatment.<sup>88</sup> Mishel,<sup>90</sup> in her reconceptualisation of the uncertainty in illness theory, explained that abiding uncertainty can dismantle the existing cognitive structures that give meaning to everyday events, throwing the person into a state of confusing and disorientation. Thus the present study's results, revealing an enduring uncertainty related to the perpetual risk of recurrence may help explain the persisting and long-term impairment of mental well-being. A finding which could support previous notions suggesting VTE should be considered a chronic illness based on the perpetual risk of recurrence.<sup>91,92</sup> Chronic illness is according with the Oxford Dictionaries defined as an illness persisting for a

long time or constantly recurring. Thus, considering the perpetual risk of recurrence VTE could possibly hold for this definition. Perhaps especially among adolescents and young adults as the risk of VTE recurrence have recently shown to be highest in the younger population.<sup>29</sup> However, the results also revealed how the young VTE patients perceived the VTE as something persisting but did not necessarily consider themselves being chronically ill. Thus, the perpetual risk of recurrence and concomitant uncertainty pose a chronic element without it necessarily being considered a chronic illness in a general understanding.

A perspective of a chronic timeline in regards of mental well-being also appeared in the strive for normalisation. The ability to feel normal was affected by the impact on everyday life and the perception of being different both as a VTE patient and socially among peers. In line with Fiandaca et al.<sup>48</sup> who reported high impairment in social activities among young patients with thrombosis, the present study demonstrated how the social ability to fit in was challenged. According to Brown et al.<sup>93</sup> the ability to fit in is important not only in terms of getting acceptance from desired peer groups but also for identity development. Thus, the ability to fit in is recognised as a key component in the developmental transition and challenges of adolescence and young adulthood. Results from the present study identified peer support from fellow VTE patients as an opportunity to feel understood. A meeting with a fellow VTE patient was experienced as reassuring and moderated the perception of feeling different and alone. Thus suggesting, peer-support, which is widely recognised, as a way to enhance well-being could show beneficial for this young group of patients.<sup>94</sup>

### **Navigating uncertainty**

The navigation of uncertainty was found central in understanding the long-term mental well-being of adolescents and young adults diagnosed with VTE. Status of the VTE, in terms of it being provoked or unprovoked, was found related to the level of uncertainty and concomitant anxiety and psychological distress. A finding in line with Klok et al.<sup>5</sup> who reported better QOL in patients with PE caused by a transient risk factor compared to patients with unprovoked PE or PE caused by permanent risk factors. Further, results of the present study elaborated on previous research into the experience of VTE which have shown worry, anxiety and psychological distress in relation to not knowing the cause of the VTE.<sup>21,49</sup> In the present study knowing the cause of the VTE was linked to the perceived chance of determining risk of recurrence. Thus the provoked or unprovoked VTE-status was linked to the chance of knowing whether or not one would experience recurrence with a potential lethal outcome. According to Mishel the hallmark of illness uncertainty is the risk of dying, which often cannot be relieved by prognostic information. In continuation hereof, Bennet et al.<sup>7</sup> have previously found that worries of future

health risk related to VTE were not moderated by beliefs about the effectiveness of medical treatment. In contrast, and in line with the findings of Casais et al.<sup>95</sup> anticoagulant treatment was identified as a protective factor in the present study. However, this did not cover situations of increased risk, where the feeling of uncertainty was described salient also years after the initial event. Findings aligned with those of Etchegary et al.<sup>96</sup> who described how travel and surgery made VTE highly salient in a group of older VTE patients. In a transition theory perspective, times of increased risk will be considered critical points entailing heightened vulnerability, reactivating a latent transition experience and state of disconnectedness.<sup>30</sup> Thus, the results indicate that uncertainty may resurface and be enhanced at times of increased risk of recurrence and be of importance for the mental well-being of adolescents and young adults diagnosed with VTE. Also in long-term, as the intensity of uncertainty may diminish during periods of relative predictability, but never completely resolve.<sup>97</sup>

Results showed the navigation of uncertainty was enhanced and complicated by delay in the initial VTE diagnosis, entailing a breach of confidence in health care professionals, and their ability to recognise symptoms of a recurrent VTE. This is in accordance with Mishels<sup>97</sup> description of how a lack of trust and confidence in the health care providers leads to higher levels of overall uncertainty, and more perceived complexity concerning treatment. In a social constructivist frame of reference, Luhmann<sup>98</sup> argues that loss of confidence increases the complexity of social systems. In the present study the increased complexity conveyed in the way, the adolescents and young adults with VTE prospectively had to relate to both the information given by the health care professionals, but also to the veracity of the information and the decisions made. This entailed uncertainty whether VTE related issues would be taken seriously. Thus self-reliance and control became essential. However, aligned with previous research the ability to be in control over future risk of VTE was considered low,<sup>7,18</sup> and self-reliance was not perceived possible when symptoms indicative of recurrence was experienced. Thus different strategies were used to in order to trust that symptoms would be taken serious, including a form of salient negotiation and exaggeration of symptoms. This finding displays an interesting paradox. On one hand the exaggeration of symptoms upholds trust for the young VTE patients that a possible recurrent event will be discovered, but on the other hand the healthcare professionals will be making their assessments on a distorted symptomatology possibly resulting in over-utilisation of healthcare services as described.

### **Perceived health threat versus illness severity**

The perception of health threat was found to play a more profound role than actual illness severity for the long-term mental well-being of adolescents and young adults diagnosed with VTE. According to Mishel,<sup>99</sup> uncertainty is a



defining experience of serious illness regardless of the specific illness characteristics. This may explain why psychological distress and increased risk of psychotropic drug purchase was observed among adolescents and young adults with relatively innocuous DVT as well as with the more serious PE, as they all have to live with the risk of recurrence and concomitant uncertainty. A finding in line with former studies reporting similar psychosocial outcomes for DVT and PE patients,<sup>6,7,18,21,49</sup> and concurrent to observations in young breast cancer survivors where initial cancer severity does not seem to affect the subsequent fear of recurrence.<sup>89</sup> Thus, the results of the present study highlight the possible importance of illness perception for mental well-being. A recognised association found in a number of other illness e.g. diabetes, congenital heart disease, cancer, and others.<sup>100,101</sup>

## **6.2. METHODOLOGICAL CONSIDERATIONS**

In the following methodological considerations will be discussed. In mixed methods research detailed and thorough descriptions of the separate qualitative and quantitative methods are encouraged, to ensure the scope of each approach is not reduced.<sup>54</sup> Thus a discussion of the multistage mixed methods framework will be followed by a discussion of the design and methods of the substudies including strengths and limitations. Similar designs and methods were used in Study 1 and Study 3, for which reason these will be discussed jointly, followed by a discussion of the design and methods of Study 2. Lastly the generalisability/transferability of results will be discussed.

### **6.2.1. MIXED METHODS**

A mixed methods study design was chosen, and through narrative weaving descriptions and joint displays of the sub-study findings, new integrated findings were revealed. This led to a better understanding of the long-term mental well-being of adolescents and young adults diagnosed with VTE. As such, the present research benefited from applying a multistage mixed methods framework. Nonetheless, a mixed methods research approach also has some disadvantages, which need to be taken into account.

Mixed methods research requires skills in qualitative, quantitative and mixed methods research. This will necessarily be more complex than conduction a single method study. In this PhD project it was therefore considered essential that the supervisors comprised different research competencies and were able to provide assistance when needed within epidemiology, statistics, phenomenology, and hermeneutics as well as Ricoeur inspired analysis and interpretation. In addition, the scope of a PhD project is limited and the advantages of mixed methods design might have been at the expense of depth of the research.<sup>54</sup> As an example, a larger epidemiological study could possibly have identified factors of importance for the long-term mental. Nevertheless,

the mixed methods design revealed important integrative findings which would not have been revealed in either of the studies alone. Thus, expanding our understanding of the long-term mental well-being of adolescents and young adults diagnosed with VTE.

Furthermore, an important point of discussion when conducting mixed method research is the combination of research methods based on fundamentally different assumptions and epistemological positions. This issue has been widely discussed within the field of mixed methods research,<sup>54,55,57,102</sup> and it has been proposed that instead of focussing on the different distinctions between the epistemological assumptions and philosophical incompatibilities, focus of attention should be on the research problem. As such, one should acknowledge and reflect on the methods' different advantages and limitations.<sup>54,59,102</sup> This point of view is supported by Brannen<sup>102</sup> who suggests that although fundamentally different there are more overlaps than differences between qualitative and quantitative methods. As such, pragmatism was employed as a philosophical underpinning for this research.

Integration is another important issue to address when conducting mixed methods research. Integration is the move beyond a use of multiple methods and a dualistic perspective.<sup>54,61</sup> Thus, it is through integration the strength and value of mixed methods research is dramatically enhanced.<sup>54,61,62,103</sup> However, mixed methods researchers have been critiqued for a lack of integration.<sup>103</sup> In the present study several measures were taken to ensure thorough and meaningful integration. Overall, a visual diagram (**Figure 1**, page 29) was used to pull together all of the components of the study and to provide an overview to ease the understanding hereof,<sup>54</sup> and thereby continually keeping the rationale for conducting the study in focus. As such, the diagram was not static but evolved over time in connection with the priorities and choices made, which were continuously considered and adjusted throughout the research process.

Integration was sought on the design and method level as well as the interpretation and reporting level. To strengthen the integration of the sub-study findings the mixed methods interpretation consisted of narrative weaving descriptions and joint displays. Joint displays are attracting more attention in the field of mixed methods research as a visual mean to both integrate and represent mixed methods results.<sup>54,62</sup> Thus, the joint displays provided structure to discuss the integrated analysis and compose the narrative weaving descriptions.

Integration in a mixed methods study also raises the potential issue of conflicting findings, in the literature highlighted as a legitimization issue.<sup>59,61,104</sup> To address the question of coherence the findings were assessed through the

fit of integration.<sup>61</sup> An example of an observed discordance was findings from Study 3 suggesting a chronic time-line perspective when comparing VTE to IDDM patients, while findings from Study 2 showed the VTE patients did not consider themselves chronically ill. Such discordance was however not considered a limitation of the present study, because of the complementary nature of the research. As such, the purpose of the mixed methods design was not to validate the findings between the sub-studies, it was to obtain a nuanced understanding of the research topic.

### **6.2.2. STUDY 1 AND STUDY 3**

Study 1 and Study 3 were designed as population-based cohort studies using historical data from Nationwide Danish registries. The main strengths of these register-based nationwide cohort studies were the large sample size, population-based coverage, and the virtually complete follow-up for psychotropic drug purchase.

The use of the Danish nationwide registries for studies in venous thromboembolism also had some limitations. In observational studies the internal validity is threatened by bias, that may occur based on issues with selection, information, or confounding,<sup>69</sup> which will be discussed below.

#### **Selection issues**

Selection bias can occur if exposure and outcome systematically differ between those included compared to those eligible for the study but not included, or from censoring caused by differential loss to follow-up.<sup>69,105</sup> However, in cohort studies selection bias will mainly concern loss to follow-up as enrolment into a cohort is only very rarely associated with outcome, because the outcome has not yet occurred at the time of entry.<sup>69,105</sup> Criteria for selection will therefore mainly impact the generalisability of the results. Information on psychotropic drug purchases, (outcome information of Study 1 and Study 3) and vital status was ascertained from the Nationwide Danish registries, which allowed for virtually complete follow-up with exception of few participants who emigrated during follow-up. Thus, the risk of selection bias arising from informative censoring caused by loss-to follow-up was negligible.<sup>105</sup>

#### **Information issues**

Results of an epidemiological study may be biased because of unreliable information.<sup>69</sup> In Study 1 and Study 3 the study population were defined by patients with a first time hospital diagnosis of VTE, identified in the Danish National Patient Register. Diagnosis in registries may not be complete or accurate, and misclassification of VTE diagnosis cannot be ruled out. Validation studies have indicated a positive predictive value of 75 %-80% for VTE diagnosis, also recently in age specific analysis of adolescents.<sup>106–109</sup>

However, the consequence of non-differential misclassification of diagnoses on risk estimates will always be in the direction towards the null-hypothesis, resulting in an underestimation of the true risk.<sup>69</sup> In other words, any misclassifications of VTE are independent of future psychotropic drug purchase and will in worst case underestimate the risk of psychotropic drug purchase. Further secondary hospital discharge diagnosis and single emergency room coded diagnoses were excluded due to the low positive predictive value hereof.<sup>106,109</sup>

In Study 3 the comparison population was defined by patients with IDDM, identified in the Danish National Patient Register and The Danish National Prescription Registry. Ascertainment of diabetes mellitus by a primary hospital diagnosis and purchase of insulin has been characterised as specific with a positive predictive value of 95%-97%.<sup>110,111</sup>

Validity of the outcome is another critical information aspect. Psychotropic drug purchase was the outcome in Study 1 and Study 3, based on claimed prescriptions in the Danish National Prescription Registry. Because of the closed-circuit character of the register only few studies have assessed the validity hereof, but data quality is perceived to be high.<sup>67</sup> Further, the effect of misclassification in terms of false negative codes would have biased the estimates towards the null. The universal reimbursement system provides a strong economic incentive for recording all drugs dispensed and dispensed prescriptions are recorded electronically.<sup>67</sup> It is though unknown whether the patients will actually take the medication, why non-compliance cannot be accounted for. However psychotropic drug purchase was in Study 1 and Study 3 used as a proxy for mental well-being, and a psychotropic drug prescription is alone an indication of mental impairment. Further, the use of psychotropic drug purchase as a proxy will likely have been an underestimation of 'true' mental impairment as other treatment options are recommended for milder cases especially among adolescents.<sup>112</sup> However, this being non-differential across the patients with VTE and IDDM as well as the age and sex matched controls in Study 1.

In the supplementary analysis of long-term anticoagulation status in Study 3, attention was towards avoiding the flawed methodological approach known as 'conditioning on the future'.<sup>113</sup> Thus, VTE patients were stratified according to anticoagulant treatment status one year after diagnosis and analysis was restricted to patients with no psychotropic drug purchase within the first year.

### **Confounding**

Confounding, in a simple definition the confusion of effects, is a concept related to studies of causality.<sup>69</sup> Study 1 and Study 3 do not reflect a causal relation between VTE and psychotropic drug purchase, but an association. Thus in

Study 1 when adjusting for the effect of ‘recent pregnancy’ and ‘recent provocations’ (including; diagnosis of cancer, rheumatoid arthritis, inflammatory bowel disease, resent trauma or resent surgery) this was not an attempt to adjust for confounding and thereby explore the causal relationship between VTE and the risk of psychotropic drug purchase. It was to ensure that risk differences were assessed between comparable venous thromboembolism cases and population controls.

Socioeconomic factors were unavailable in Study 1 and Study 3, which could be a limitation when investigating VTE and mental well-being. Low socioeconomic position has shown to influence the risk for VTE, and is generally associated with increased mental health problems. Moreover, it has been associated with decreased QOL in women with pregnancy-related DVT. Another limitation which cannot be ruled out is that the same inciting event caused both the VTE and the impaired mental-wellbeing. Finally given that VTE patients are regularly in contact with primary healthcare, they may likely receive diagnosis and treatment for other medical conditions, including mental health problems; therefore, they may receive more psychotropic drug prescriptions.

These could all be important limitations if the focus of the study was on the causal relation between VTE and psychotropic drug purchase. That VTE caused impaired mental health. However, as the intent of this mixed methods study was to gain a compressive view of the long-term mental well-being of adolescents and young adults diagnosed with VTE confounding by these factors are not an issue of concern. Although still interesting and relevant to explore in future research.

### 6.2.3. STUDY 2

A qualitative design using semi-structured interviews and a phenomenological hermeneutical approach inspired by the French philosopher Paul Ricœur was applied in Study 2. In the following methodological considerations will be discussed using the scientific criteria of *reliability* and *validity*.<sup>74,114,115</sup>

#### Reliability

Reliability pertains to the consistency and trustworthiness of the research findings<sup>74</sup>, and is relevant to discuss in relation to *participant observation and interviewing, transcriptions and translation, and analysis and interpretation*.

In studies based on participant observations and interviews the researcher is the primary instrument for gathering data. Therefore, the reliability of the researcher is important to discuss. An open approach was sought in the participant observations and interviews and it is relevant to consider the

possible affect the researcher's pre-understanding could have had on the generated data. Based on the researcher's background as a registered nurse presumptions and leading questions, although unintended, could increase the risk of reproducing common sense knowledge.<sup>74</sup> However, the researcher had limited clinical experience in the specific field of research, why a potential skewing will have pertained to knowledge on a more general level. Further, the research strategy entailed reflexivity throughout the research process which guided systematic and critical reflection. As such, reflection on reliably started before the participant observations and continued throughout the development of interview-guides and the conduction of interviews, in continued discussion with the supervisors. This did not prevent the researcher from affecting the research process but formed the basis for considerations on how it was affected, thus which preconceptions must be taken in relation to the formed conclusions<sup>114</sup>. Further, in the interview situation open-end questions were asked withholding interoperation of meaning and only asking elaboration questions when needed for the interview to continue.

The accuracy of transcriptions and translations is another important factor in an interview study.<sup>114</sup> To enhance the reliability of the transcriptions, the interviews were transcribed verbatim by the researcher directly after they were conducted. To ensure the text would stand as close to what was said as possible, limited punctuation was used and distinct pause for thoughts were marked. Further, if words were unclear, no guesses were made. Because the study was conducted in Denmark translation posed a particular challenge and several measures were taken to ensure trustworthiness.<sup>116</sup> The transcription and analysis of the interviews were conducted in Danish before translating the quotations and the short stories into English. Further translation fidelity was sought in a discussion between the Danish and English speaking authors determining the context and relevance including forward-backward translation.<sup>116</sup> Finally, the meaning was examined in the source and target language with help from a professor of language and translation revision.

The reliability of a study also depends on whether the analytical strategy is well prepared and well documented. The analytical strategy was inspired by Ricœur's interpretation theory, which is considered well-established within the caring science. A Ricœur inspired interpretation and analysis has been widely used and is recognised as a fruitful method to investigate 'lived experience'.<sup>79,117</sup> A strength in applying this method is that it requires explicit and thorough argumentation. According to Ricœur there will always be more than one way to interpret a text, and it is the argumentation which gives credibility and validity to the interpretations.<sup>77</sup> As such, this is considered a good basis for a well-documented analysis. In Study 2 the argumentation for the credibility and validity of the interpretation was rendered visible by

exemplifying, how the three analytical levels were performed in NVivo. Hereby providing transparency in the analytical process for the reader.

### **Internal Validity**

Validity refers in common language to the truth, correctness and the strength of a statement. In qualitative research a broad view of internal validity pertains to whether a method investigates what it is intended to investigate.<sup>74</sup> As such, an important issue to discuss is sampling, as it affects the quality of the data sources. A maximum variation sampling strategy was applied, which allowed for multiple perspectives and complexities of the lived experience of VTE to be revealed. This was considered a strength of the study, in light of the objective of obtaining in-depth understanding of the long-term mental well-being. However, recognising that inclusion of e.g. ethnic and racially diverse participants may have nuanced and broadened the understanding even further.

The creation of the short stories across the 12 interviews is also relevant to discuss in relation to the internal validity of Study 2. When creating stories across the interviews the researcher risk losing credibility, by creating stories too far from the narrated experiences of the participants.<sup>118</sup> However, the short stories were not something made up, but consisted of examples originated in the interview quotes. Thus, what the stories posed was a re-description of the reality of the quotes, which along with the use of poetic language facilitated a articulation of the deepest essence of the meaning.<sup>79</sup> In relation to this it is also argued that the re-writing and de-contextualising of the data into stories there might be a risk the story is no longer recognisable to the participant. However, as Morse<sup>115</sup> argues it is not the participants' job to validate findings. It is the researchers' responsibility to ensure the research is credible transferable and dependable. In line with this Ricœur<sup>76</sup> argued that when a text is written down it is separated from the mind and the intention of the narrator, and thus opened for interpretation. It is therefore not the intention of the author that is pursued but a deeper understanding of what the text refers to in the world. Thus, what was sought was not what the young VTE patients believed they were saying but an objective description of their lived experiences.

### **6.2.4. THE GENERALISABILITY AND TRANSFERABILITY OF THE RESULTS**

The external validity; the extent to which the results of the study could be extrapolated to other populations than the study population, in quantitative research referred to as generalisability and in qualitative research often referred to as transferability, could be affected by several things.<sup>69,114</sup>

Denmark is historically a racial and ethnically homogeneous society, which reflected in a non-ethnically diverse study-sample in Study 2 and will accordingly have reflected in the populations of Study 1 and Study 3.<sup>66</sup> Generally, QOL and prevalence of mental health problems varies by ethnicity and race.<sup>119,120</sup> Thus, the results may not be generalisable to more diverse VTE populations, and it could be argued that a variation in race and ethnicity might have broadened the understanding of the long-term mental well-being post VTE. Furthermore, the results will reflect the culture norms and values of young Danes as the study was conducted in a Danish context. Cultural differences in regards of family and social relations, planning of parenthood and alcohol consumption are recognised among adolescents and young adults across the globe, also among the Western countries.<sup>121</sup> This might affect the generalisability of the results, and suggests further exploration of the long-term mental well-being of adolescents and young adults diagnosed with VTE in other countries and within racially and ethnically diverse groups.

The defined age-range poses a recognised limitation in regards of generalisability. There is currently no standard definition of adolescence and young adulthood and the varying and arbitrary choices of age-range is acknowledged as a limit to the comparability of research covering adolescents and young adults, nationally as well as internationally.<sup>40,53</sup> Definitions beyond a chronological defined age-range have been proposed considering factors such as physical, social, and cognitive development<sup>8,40</sup> However, these often show difficult to apply for research purposes e.g. in epidemiological studies such as Study 1 and Study 3. Age was therefore chronological defined in the present study. Nevertheless, the chosen age-range build upon reflection on the developmental tasks and transitions of adolescents and young adulthood. Thus, ranging from mid-puberty until independent and self-supporting adulthood, which may enhance the generalisability of the results.





## CHAPTER 7. CONCLUSION

The aim of this multistage mixed methods study was to investigate the long-term mental well-being of adolescents and young adults diagnosed with VTE. This was sought through; epidemiological descriptions of the long-term mental well-being using psychotropic drug purchase as a proxy; qualitative exploration of the lived experiences following VTE; epidemiological comparisons of the long-term mental well-being between adolescents and young adults with VTE and IDDM and finally; an integrated mixed methods interpretation combining the description, exploration and comparison.

In conclusion:

- The mental well-being of adolescents and young adults was negatively impacted in long-term when considering psychotropic drug purchase as a proxy. One in five adolescents and young adults diagnosed with VTE redeemed a psychotropic drug prescription within the first 5 years after diagnosis. A risk double than of age and sex matched peers.
- VTE was perceived as something that would always lie in wait. Youth immortality was lost and mortality was salient in life following VTE. This manifested particularly in fear of VTE recurrence and the experience of living with a body in a state of alert. A perception of being different both among peers and patients diagnosed with VTE was prominent, and resulted in a feeling of loneliness. Furthermore, a pronounced insecurity in terms of symptom management was evident in life after VTE, amplified by a delayed diagnosis, and concomitant loss of confidence in health care professionals.
- The long-term mental well-being of adolescents and young adults diagnosed with VTE was worse than that of chronically ill patients with IDDM when considering risk of psychotropic drug purchase as a proxy.

Integrated:

- The mental well-being of adolescents and young adults diagnosed with VTE had a chronic perspective with an increased risk of psychotropic drug purchase and psychological distress persisting over time. Impaired mental well-being largely connected to fear of recurrence and concomitant uncertainty, but also to a strive for normalisation, where the ability to feel normal was restricted by a perception of being different and an impacted everyday life.

- To navigating uncertainty was important for the long-term mental well-being. The level of uncertainty was related to the provoked or unprovoked status of the VTE, as having a cause for the VTE was linked to the chance of determining risk of recurrence. Anticoagulation therapy represented another key aspect in relieving uncertainty. Nevertheless, this did not cover situations of increased risk of recurrence where uncertainty resurfaced and was enhanced also years after the VTE event. Uncertainty was enhanced and complicated by a delay in diagnosis entailing a breach of confidence in healthcare professionals and their ability to recognise symptoms of recurrence. Thus control and self-reliance was essential.
- Perceived health threat played a more profound role than illness severity for the long-term mental well-being. Both patients with DVT and patients with PE experienced psychological distress related to possible recurrence and the potential life threat.

## CHAPTER 8. IMPLICATIONS AND PERSPECTIVS

This research highlights the clinical importance of long-term focus on mental well-being in adolescents and young adults diagnosed with VTE. Rehabilitation including a psychosocial effort focused on detecting and treating anxiety and depression is widely recommended within cardiac diseases such as coronary heart disease or heart failure by both The European Society of Cardiology, the American Heart Association and the American College of Cardiology.<sup>122,123</sup> However, within the field of VTE, rehabilitation have received very limited attention. The present research encourages the inclusion of mental well-being when developing rehabilitation programs in the field of VTE. However further research is needed to establish the form and extent of this. In line of this, it would be relevant to explore possible variations across clinical subgroups e.g. provoked or unprovoked VTE or in terms of socioeconomic status.

VTE is not traditionally considered a chronic condition. However, the indication of long-term impairment of mental well-being primarily related to fear of recurrence support previous notions of considering VTE a chronic condition<sup>91,92</sup>. Perhaps VTE is better characterised as a chronic condition, owing to the high risk of recurrence, post thrombotic syndrome and complex long-term management of anticoagulant treatment, at least for some. This would allow a different focus in the disease management and provide access to certain benefits and services. However, this could also lead to inexpedient pathologisation. Therefore, further research exploring the management of VTE in a chronic perspective would be relevant.

Further, the present research indicates that peer support could show beneficial for mental well-being of adolescents and young adults diagnosed with VTE. However, there are numerous different models of peer support ranging from professionally-led peer support groups to peer-led support groups, from face-to-face meetings to internet-based peer support.<sup>124</sup> Thus, further work is required to identify if one model would be more beneficial than another.

Finally, the perception of future health threat may be more important than actual illness severity, for the long-term mental well-being. Thus, the present research suggests that focus on illness perception could show more relevant than VTE-status (DVT, LE). This also highlights the potential role of age; as previous illness experience will reflect in the illness perception. In the absence of previous illness experience patients will lack the skills to help them face illness uncertainty, leading to psychological distress.<sup>90</sup> As such, illness experience may play an important role for long-term mental well-being, also

in older VTE patients with limited illness experience. Further exploration of the role of illness experience is needed.

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# APPENDICES

**Appendix A.** Information letter to health professionals

**Appendix B.** Example of interview guide

**Appendix C.** Information letter to participants



## Appendix A. Information letter to health professionals

AALBORG UNIVERSITETSHOSPITAL

### Information om undersøgelse:

#### *Konsekvenser af venøs tromboembolisk sygdom som ung eller ung voksen*

Venøs tromboembolisk sygdom (VTE) (samlet betegnelse for DVT og lungeemboli) er en hyppig og potentiel dødelig sygdom. Sygdommen er mest almindelig i den ældre befolkning, og viden om VTE hos unge og unge voksne er derfor begrænset. Hvert år bliver 450 personer i Danmark mellem 13-33 imidlertid ramt af VTE, og generelt ved man at VTE kan påvirke patientens fysiske, psykiske og sociale velbefindende. De unge vil potentielt skulle leve med denne påvirkning i en lang årrække, hvilket sandsynligvis kan have betydelige konsekvenser for dem. I hvilken grad dette er tilfældet er dog uvist.

Formålet med denne undersøgelse, som er del af et større Ph.d. projekt, er derfor at opnå indsigt i, hvordan unge patienter oplever deres liv efter at være blevet ramt af VTE.

På den baggrund håber jeg at kunne inkludere patienter med VTE i alderen 13-33 år fra afdelinger i hele Region Nordjylland. Undersøgelsen i denne del af ph.d. projektet består af, at jeg vil følge patienten under indlæggelsen og udføre nogle generelle observationer. Herefter vil jeg 6 til 12 måneder efter udskrivelse udføre dybdegående interviews med patienten i patientens eget hjem.

Jeg vil derfor meget gerne kontaktes på tlf.: 29 29 91 14, hvis I modtager eller har en patient med VTE indlagt.

Hvem jeg er:

Jeg er uddannet sygeplejerske, og har en kandidatgrad i sygepleje (cand.cur.) fra sommeren 2012. Jeg er ansat som ph.d.-studerende ved Trombosecenter Aalborg og Forskningsenhed for Klinisk Sygepleje. Denne undersøgelse er en del af mit ph.d.-projekt, hvor jeg undersøger det langsigtede mentale velbefindende hos personer diagnosticeret med VTE som ung eller ung voksen. Ph.d. projektet vejledes af Forskningsleder, lektor, cand.cur., ph.d. Erik Elgaard Sørensen og Specialeansvarlig overlæge, lektor, ph.d. Torben Bjerregaard Larsen og forventes afsluttet i 2015.

Har du spørgsmål til undersøgelsen, er du meget velkommen til at kontakte mig.

De bedste hilsner  
Anette Arbjerg Wind

#### Kardiologisk Afdeling, Trombosecenter Aalborg

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Anette Arbjerg Wind

E-mail: [a.wind@rn.dk](mailto:a.wind@rn.dk)  
Tlf.: 29 29 91 14

## Appendix B. Example of interview guide

### Interviewguide

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#### *Indledende*

---

Tak fordi du vil deltage. - Interviewet er frivilligt og det vil blive optaget.

Der er ikke nogle rigtige og forkerte svar og jeg leder ikke efter noget specielt eller et specifikt svar.

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#### *Generelle spørgsmål*

---

#### *Individuelle spørgsmål*

---

Vil du fortælle mig om det at have haft en blodprop?

Du beskrev for mig i vinters, at du havde været i kontakt med lægen inden de finder ud af, at det er en blodprop, vil du fortælle mig lidt mere om det?

Hvordan har du oplevet det?

Hvilke betydning har det haft for dig?

Du fortalte mig at, at du følte det var mærkeligt at være indlagt, da du ikke følte dig "rigtig" syg. Vil du fortælle mig lidt mere om det?

Er der noget, som har ændret sig positivt/negativt?

Hvilken betydning har det for dit liv i dag?

Vil du fortælle om blodproppen betydet noget ift. hvad du gør eller ikke gør?

Vil du fortælle om, hvordan du oplever det, når du mærker noget der minder om blodproppen?

Er der noget, som har kunne gøre dig nervøs eller usikker efter ud har haft en blodprop?

Vil du fortælle om, hvordan dine omgivelser reageret (venner, familie)?

Hvad har været betydningsfuldt for dig i tiden efter blodproppen?

Hvis en du kendte/en af dine venner fik en blodprop var der så noget specielt du ville ønske for dem?

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#### *Afrunding*

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Afrunding - Jeg har ikke flere spørgsmål, er der noget du vil tilføje?

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## Appendix C. Information letter to participants

AALBORG UNIVERSITETSHOSPITAL

### Undersøgelse af unge og unge voksnes oplevelse af at have haft en blodprop i lungen eller benet

Hej!

Som led i et forskningsprojekt der undersøger, hvilke konsekvenser det kan have, at man som ung eller ung voksen har haft en blodprop i lungen eller benet, håber jeg, at du har lyst til at deltage i en interviewundersøgelse.

Hvorfor:

Der findes i dag en begrænset viden om, hvordan man som ung oplever livet efter at have haft en blodprop i lungen eller benet, og om det har konsekvenser for én. Det kan derfor være svært at vide, hvordan man bedst hjælper unge mennesker i din situation.

Projektets formål er derfor at opnå viden om konsekvenserne af at have haft en blodprop som ung, så man kan forbedre mulighederne for at hjælpe dig og andre unge, der bliver ramt af en blodprop i lungen eller benet.

Undersøgelsen består af, at jeg under din indlæggelse/kontakt til hospitalet vil være tilstede og overvære nogle af de samtaler du har med sygeplejerskerne og lægerne. Mellem 6 og 12 måneder efter din udskrivelse vil jeg kontakte dig igen, og spørge om lov til at lave et interview med dig. Interviewet kan enten foregå hjemme hos dig eller på sygehuset afhængig af, hvor du helst vil mødes.

Det er helt frivilligt om du har lyst til at deltage i undersøgelsen og din beslutning får ingen indflydelse på din behandling eller dit forløb generelt. Siger du ja til at deltage i undersøgelsen, kan du til enhver tid trække dit samtykke tilbage og udgå af undersøgelsen. Oplysningerne du giver videre til mig vil efter en analyse og fortolkning indgå som en del af forskningsprojektet. Alle oplysninger vil blive behandlet anonymt, forstået på den måde, at du ikke vil kunne genkendes.

Hvem jeg er:

Jeg er uddannet sygeplejerske, og har en kandidatgrad i sygepleje (cand.cur.). Jeg er ansat som ph.d.-studerende ved Trombosecenter Aalborg, hvilket er en del af Kardiologisk Afdeling ved Aalborg Universitetshospital. Denne undersøgelse er en del af mit ph.d.-projekt, som forventes afsluttet i 2015.

Hvis du har spørgsmål til undersøgelsen, er du meget velkommen til at kontakte mig.

De bedste hilsner

Anette Arbjerg Wind

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